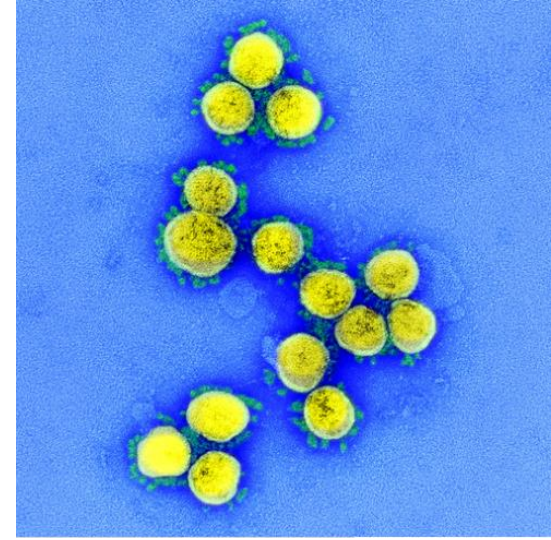


28 August 2021



THE IMMUNE SYSTEM: INTRODUCTION & BASIC CONCEPTS


Margarita del Val

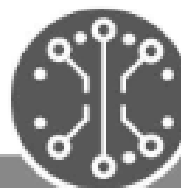
Viral Immunology


Centro de Biología Molecular Severo Ochoa (CSIC-UAM)


RESEARCH

Coordination of over 330 research groups from 91 CSIC Institutes with over 110 funded grants to confront the coronavirus pandemic from all sides

TD.  **Tratamiento y Análisis de Datos: Inteligencia Artificial**

TT.  **Transferencia de Tecnología**

TI.  **Compartiendo Información**

TA.  **Coordinación Autónoma**

6. MEDIOS, DIVULGACIÓN Y EDUCACIÓN

- **Imagen de la ciencia**
- **Comunicación social:** lucha 'fake news'
- **Divulgación:** ayudar a comprender la enfermedad
- **Educación obligatoria en Salud global:** protocolos de prevención, protocolos de contención; estilo de vida, alimentación

5. IMPACTO

- **Social**
- **Político:** instituciones, organizaciones internacionales
- **Económico**
- **Impactos medioambientales**
- **Impacto en Dinámicas científicas y de innovación**

4. TRATAMIENTO

- **Nuevos antivirales**
- **Reposición de fármacos**
- **Anticuerpos terapéuticos**
- **Vacunas**
- **Inflamación**

1. PREVENCIÓN

- **Origen:** Historia; Cambio Global
- **Diseminación del virus**
- **Protocolos de prevención:** protección; vacunas; educación y estilo de vida
- **Prevención económica**

2. ENFERMEDAD

- **Estructura del virus**
- **Genética de virus**
- **Infección y gravedad:** factores agravantes y genéticos
- **Respuesta inmune**

3. CONTENCIÓN

- **Propagación y epidemiología**
- **Diagnóstico y detección**
- **Protección:** equipos, formación...
- **Protocolos de contención:** canales de comunicación y cooperación científico-institucionales

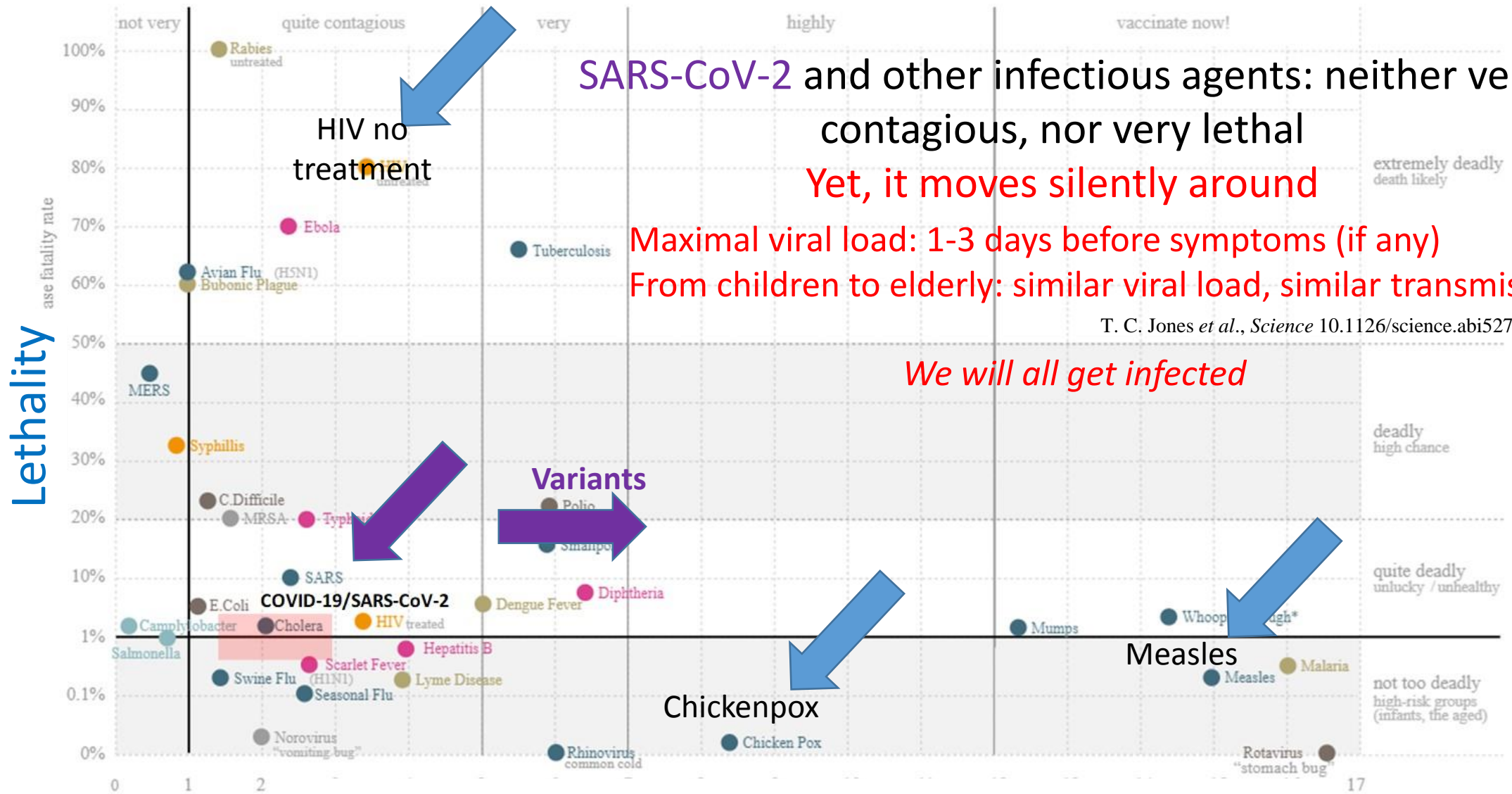


THANKS TO DONORS!

SARS-CoV-2:
The virus

The Microbe-scope

PRIMARY TRANSMISSION METHOD airborne bites body fluids fecal-oral food sexual contact surfaces

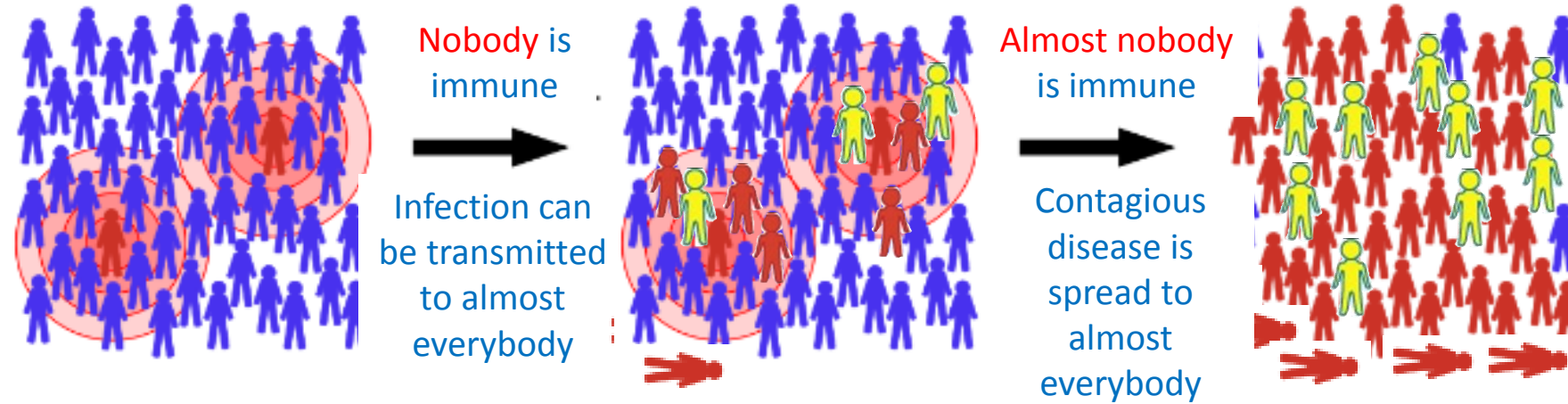


T. C. Jones et al., Science 10.1126/science.abi5273 (2021).

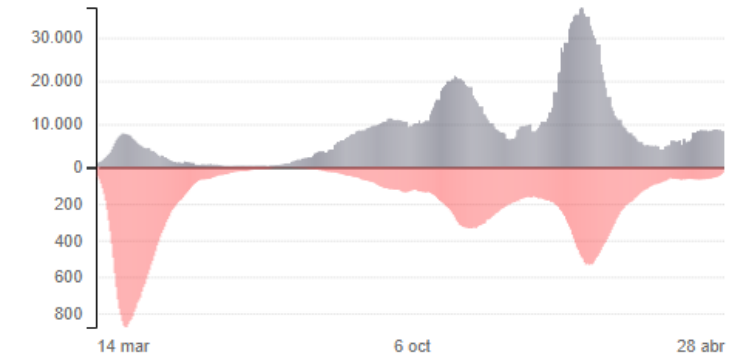
Transmissibility, basic reproduction number, R_0

Why this pandemic with SARS-CoV-2 Coronavirus ?

Nobody had **any** immunity



Evolución de casos diagnosticados y muertes (media 7 días)



Fuente: Ministerio de Sanidad e ISCIII * Actualizado 29/04/2021

El Confidencial

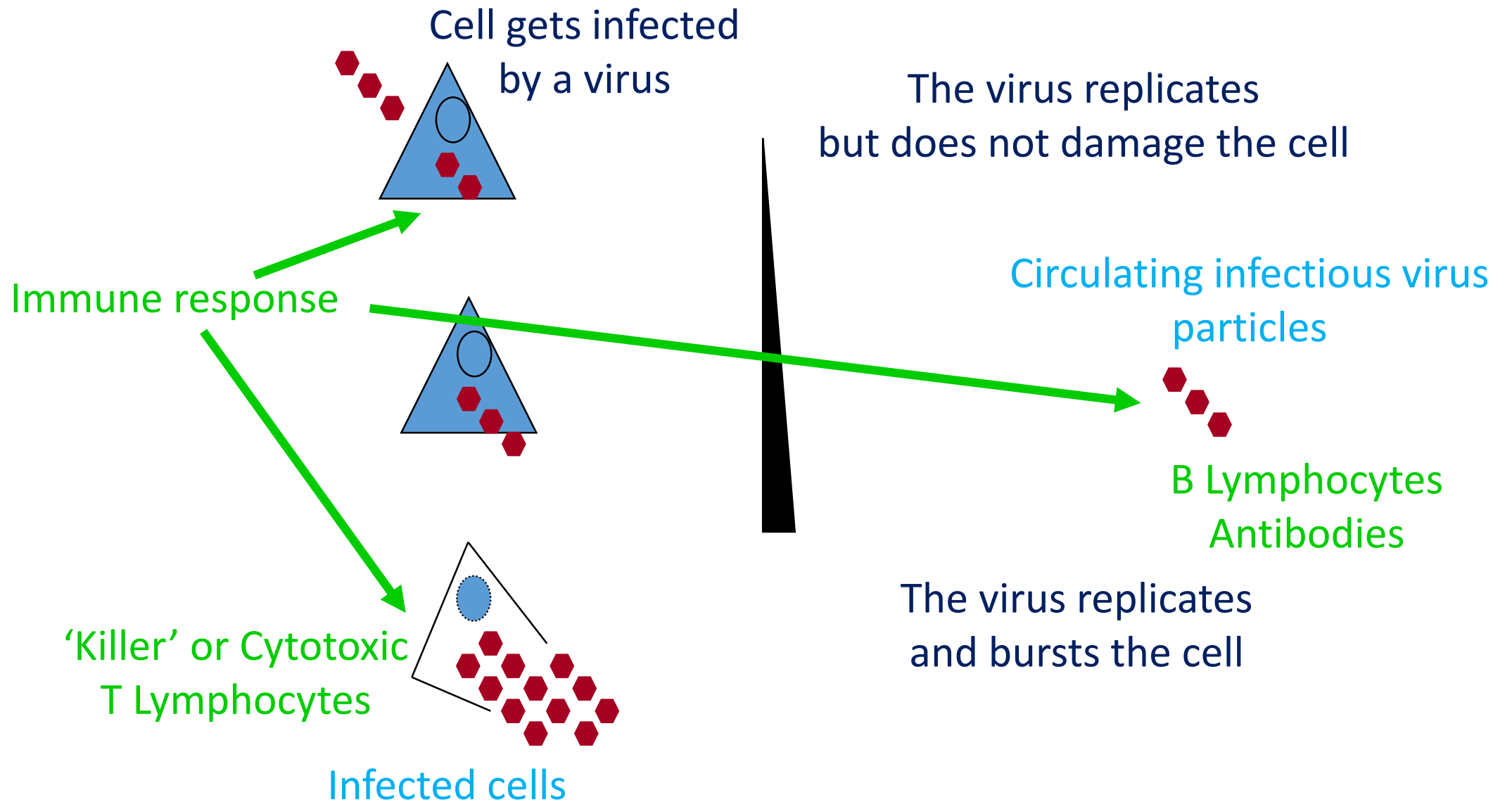
June 2020, ENE-COVID19 massive, representative, antibody detection in Spain:

Only 5% of the population had immunity

August 2021: estimated: 21% natural immunity + 68% fully vaccinated: already / still only **~75% immune** population

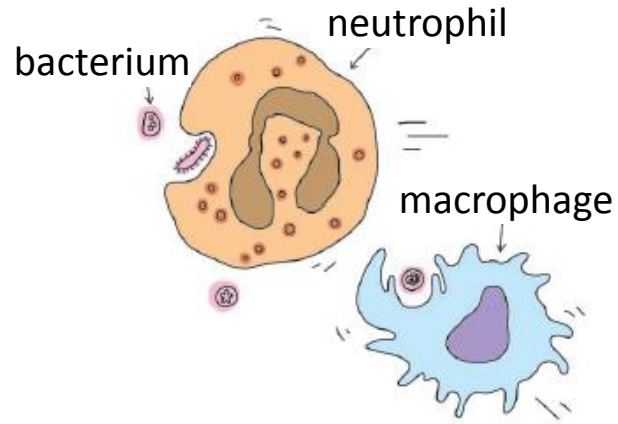
(2 doses, till 27/08/21, https://quemasqueremos.shinyapps.io/Shiny_pre/)

The immune system look at viruses



Our immune system eliminates **foreign and harmful agents**

1st: eat them up as they come in

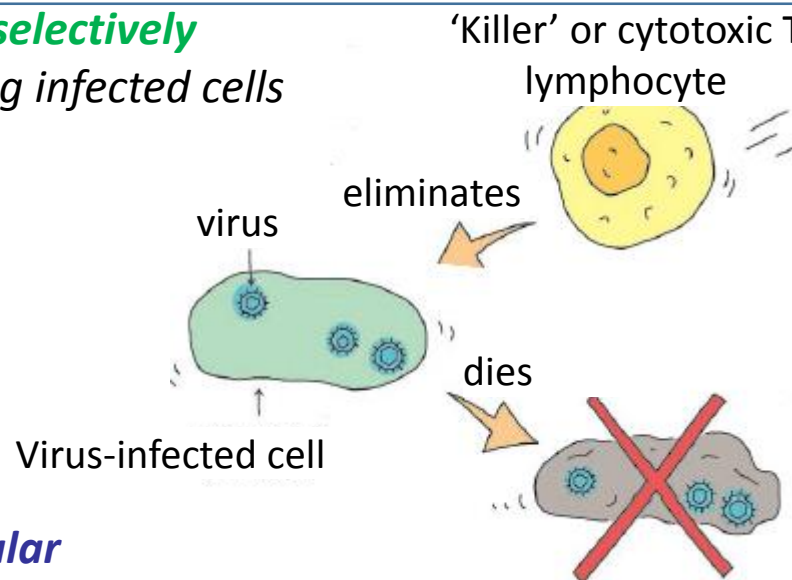


Innate
Immune
Response

the “city Police”

Our immune system is our best self-defense against the coronavirus

2nd: **selectively**
killing infected cells



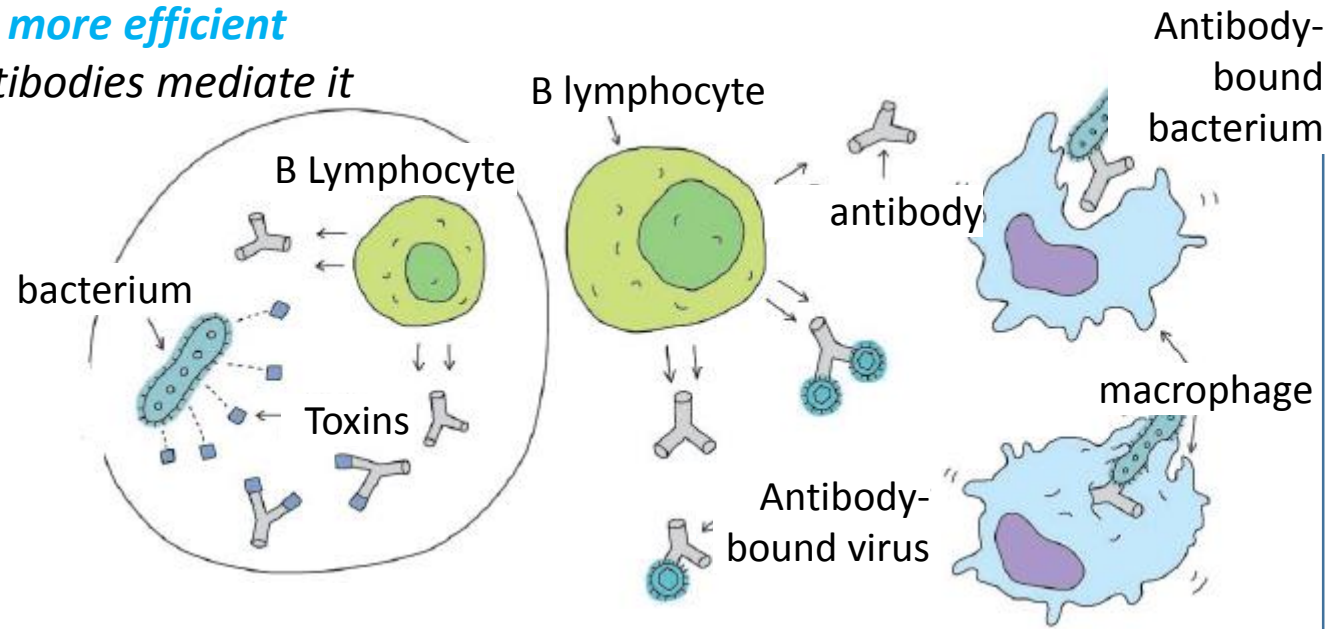
Cellular
Immune response

the “èlite units”

They eliminate virus-infected cells, where the virus multiplies rapidly

more “èlite units”: antibodies

3rd: phagocytosis turns **more efficient** and **selective** when antibodies mediate it



Humoral
Immune Response

Antibody-bound virus

Antibodies neutralize circulating virus particles, so they cannot infect new cells

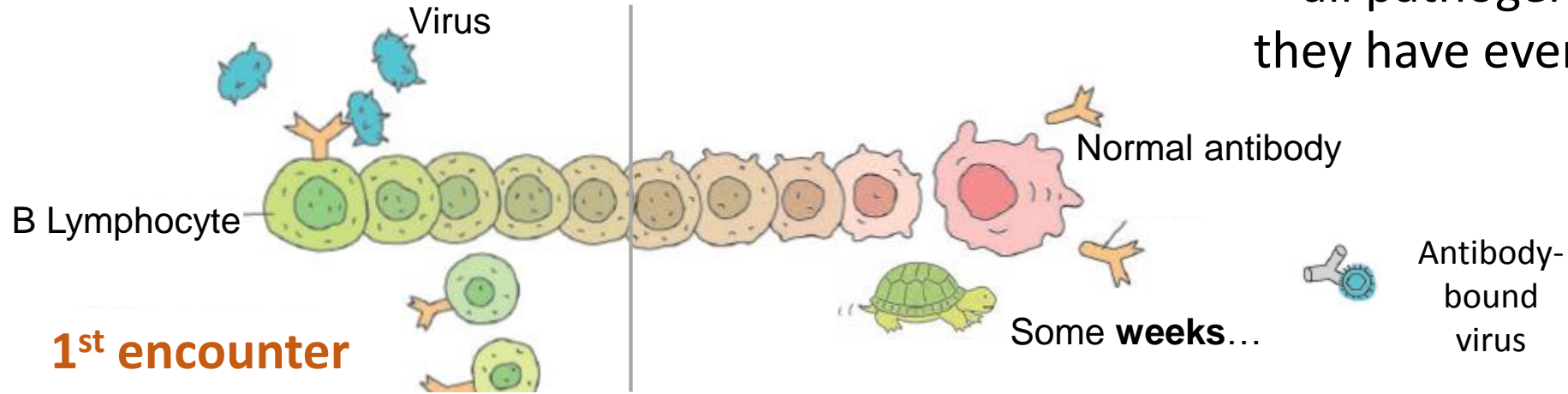
Naive unexperienced B lymphocytes
- Make IgM antibodies

Mature, experienced B lymphocytes
- Make IgG antibodies

Intrinsic diversity of the **primary** antibody response: **each single person has a personal repertoire** of antibody sequences ready to go in her unexperienced B lymphocytes

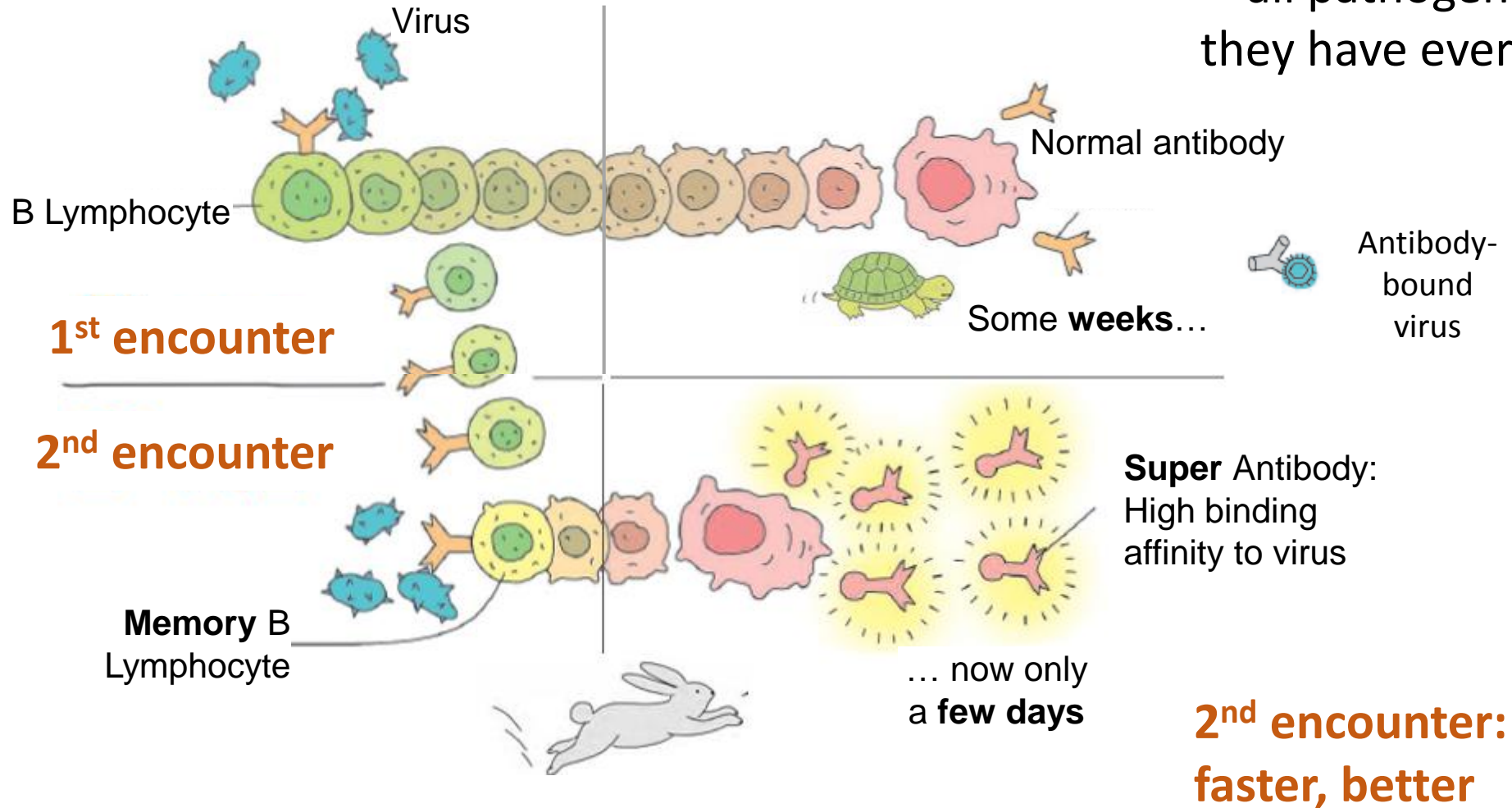
Why do many infectious diseases never come back in a person?

Our lymphocytes **learn** and **remember**
all pathogenic microbes
they have ever encountered



Why do many infectious diseases never come back in a person?

Our lymphocytes **learn** and **remember**
all pathogenic microbes
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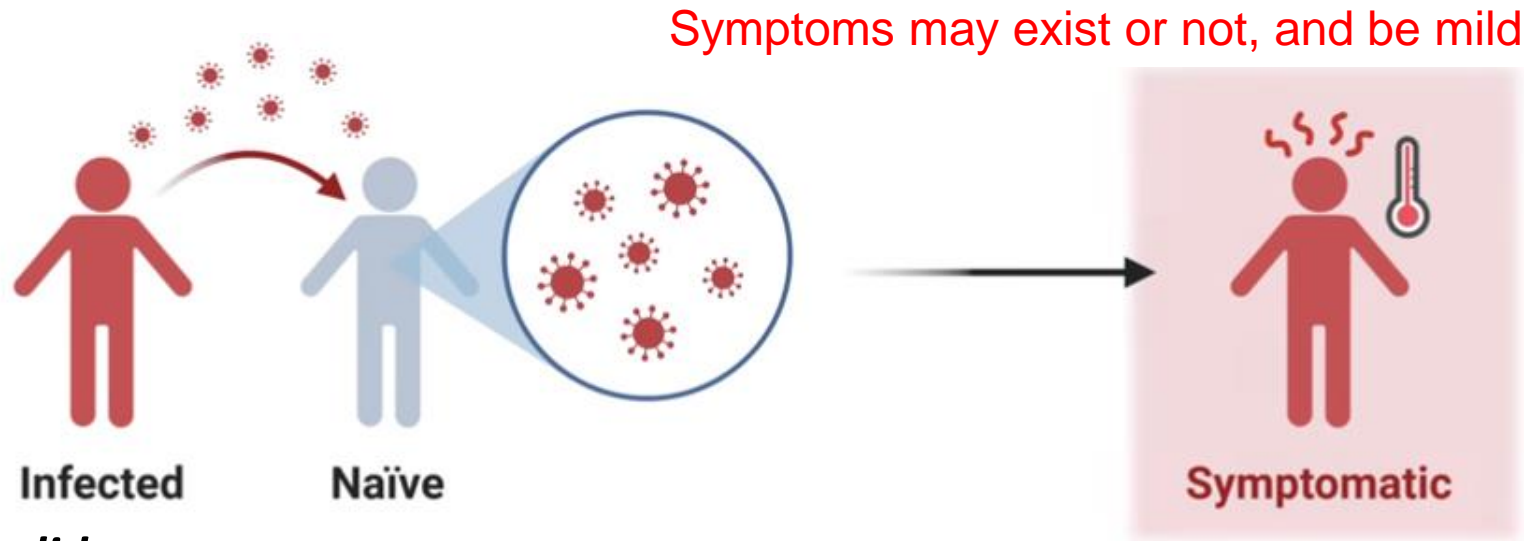
2nd encounter:
faster, better

Immune MEMORY is the basis for vaccines

Immune MEMORY

B and T lymphocytes, the elite cells that mediate long-lasting protection from re-infection

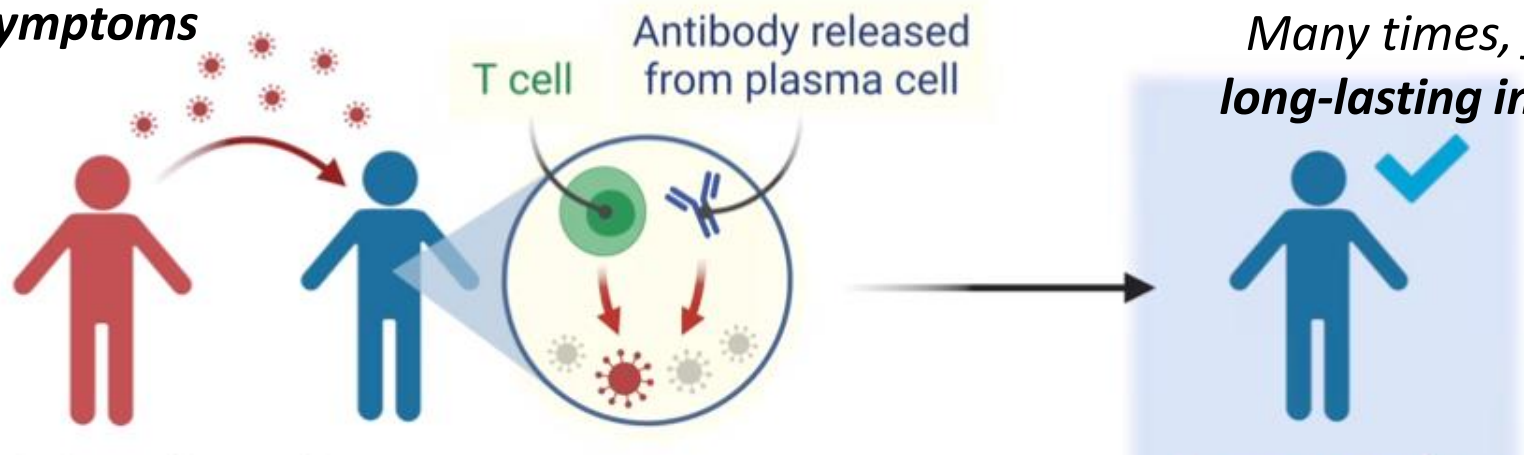
People who have never encountered the virus (all humankind)



Symptoms may exist or not, and be mild to severe

Immunity after natural infection is solid, and confers ~97% protection from symptoms

People who already have encountered the virus (have suffered the infection and survived) (or have been vaccinated)



Many times, for ever: long-lasting immunity

Symptoms are mild or absent

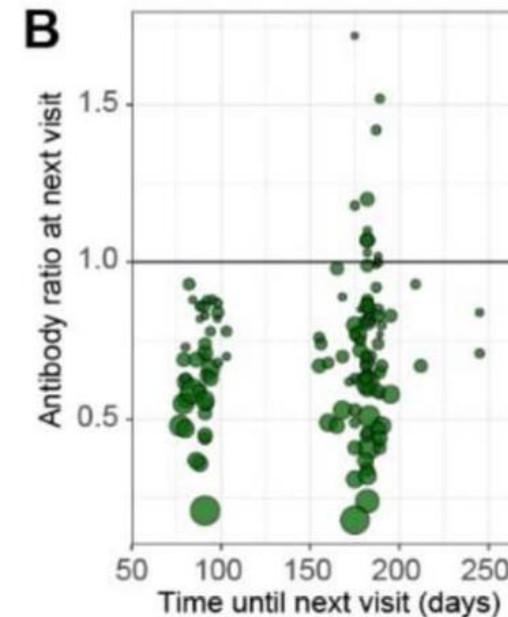
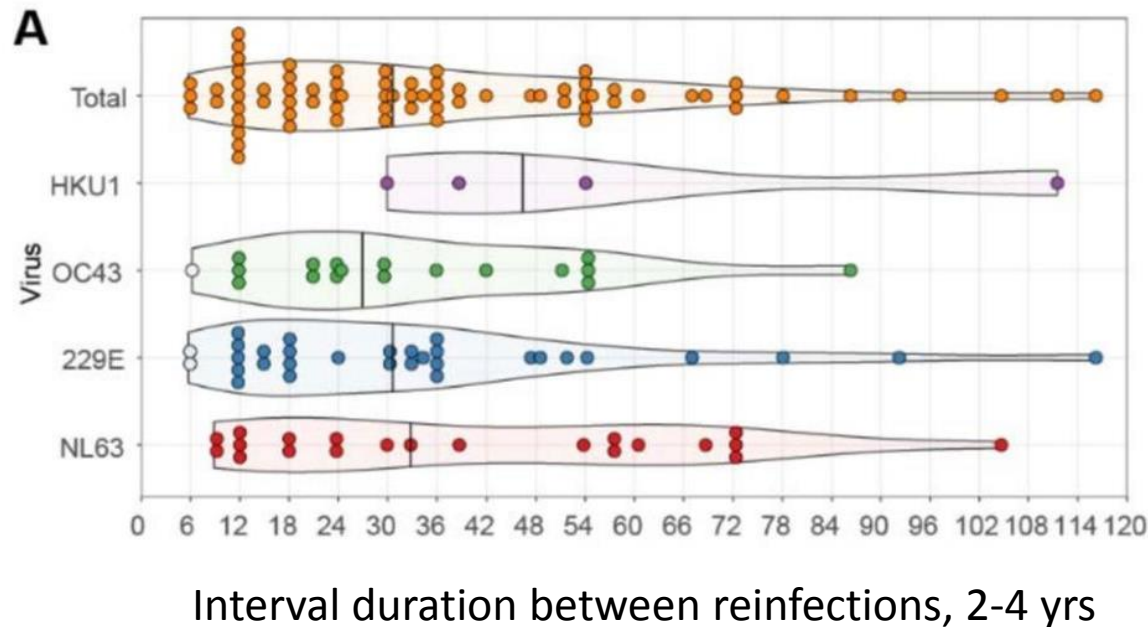
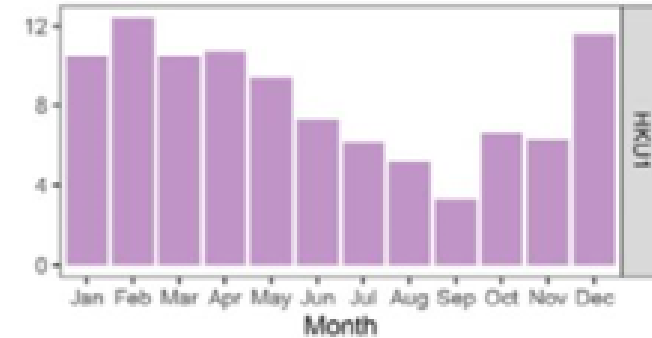
Common cold coronaviruses cause 10-15% of common colds: they also **contain virulence genes**

As **everybody** has certain immunity since childhood:

- they seem **benign**
- they are **seasonal**

Immunity to common cold coronaviruses is also good but not optimal.

Antibodies also wane with time, yet protection is good enough.



Most decrease, but some also present an **antibody boost** after reinfection

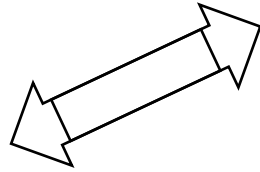
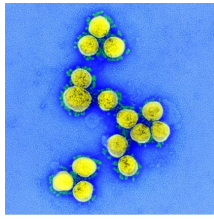
Seasonal coronavirus protective immunity is short-lasting

Edridge et al *Nat medicine*

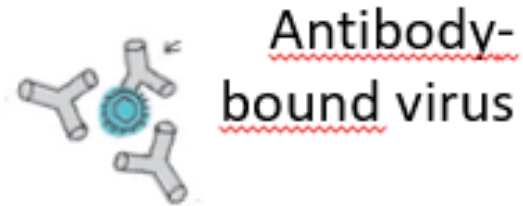
<https://doi.org/10.1101/2020.05.11.20086439>

Figure 1 Infection and reinfection characteristics, and waning immunity for seasonal coronaviruses.

SARS-CoV-2 coronavirus
is not the worst infectious enemy ever
... had we got infected as children



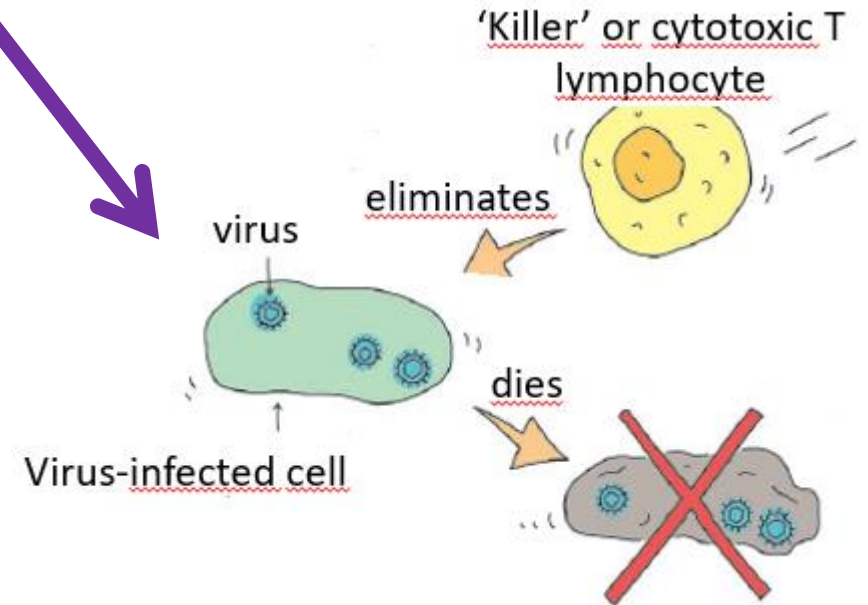
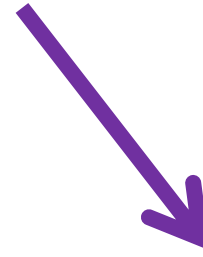
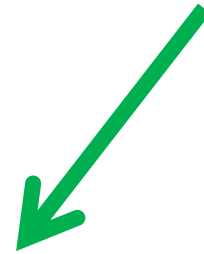
The problem is we had / have no barriers: Complete
lack of cellular and humoral immunity in humankind



Humoral immunity:

Neutralizing antibodies block infectious
virus particles.

They recognize **variable** regions
(epitopes) on **exposed** viral proteins



Cellular immunity:

Cytotoxic T lymphocytes destroy
virus-infected cells, the viral factories.
They recognize **any region** (epitope)
of **any viral protein**

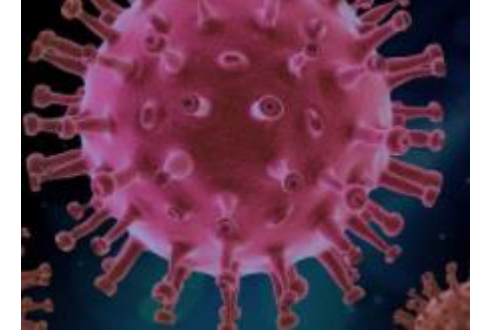
Vaccine
mRNA
or
Adeno



Vaccines based only on the S protein

SARS-CoV-2 virus

Natural infection



Humoral immunity:

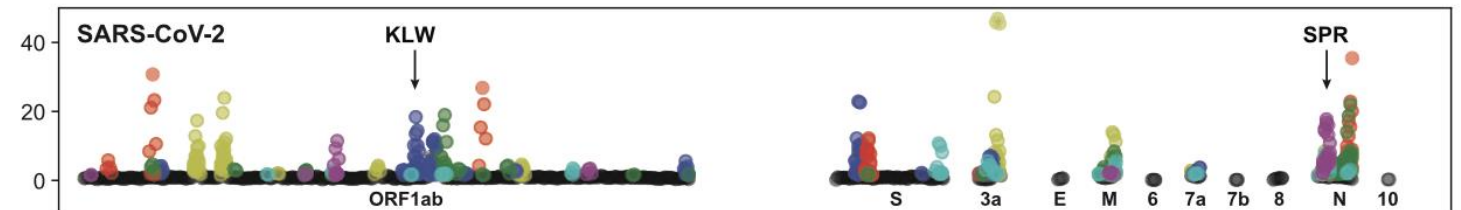
Antibodies to **exposed variable** areas of the S protein

After full vaccination, a later infection is mild, and reinforces immunity to S... and to all other viral proteins. Virus control turns easier

Cellular immunity:

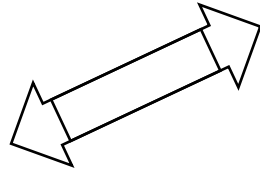
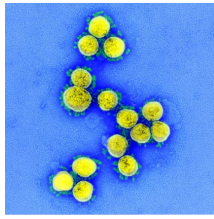
Lymphocytes specific for **any** viral protein

The 2nd dose reinforces immunity to S protein and controls the virus

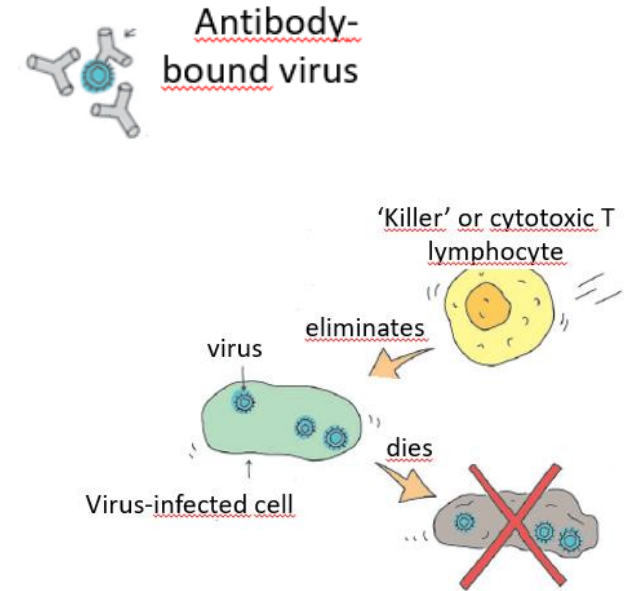


Immunity to viral infection is also long-lasting, and broader in specificity – *but the risk is 100 to 100.000 times higher than any vaccine*

SARS-CoV-2 coronavirus
is not the worst infectious enemy ever
... had we got infected as children



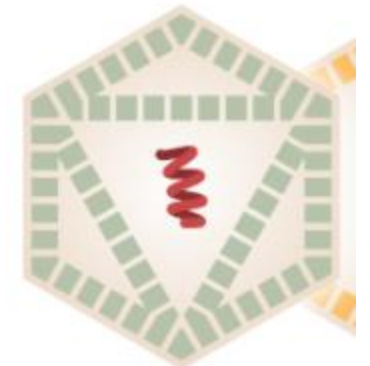
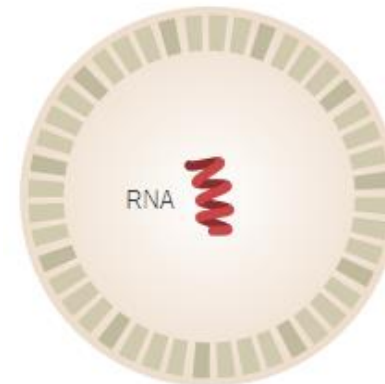
The problem is we had /
have no defense: Complete
**lack of cellular and humoral
immunity** in humankind



- Primary infection entails no problem for those with a strong and
balanced immune systems: Young people

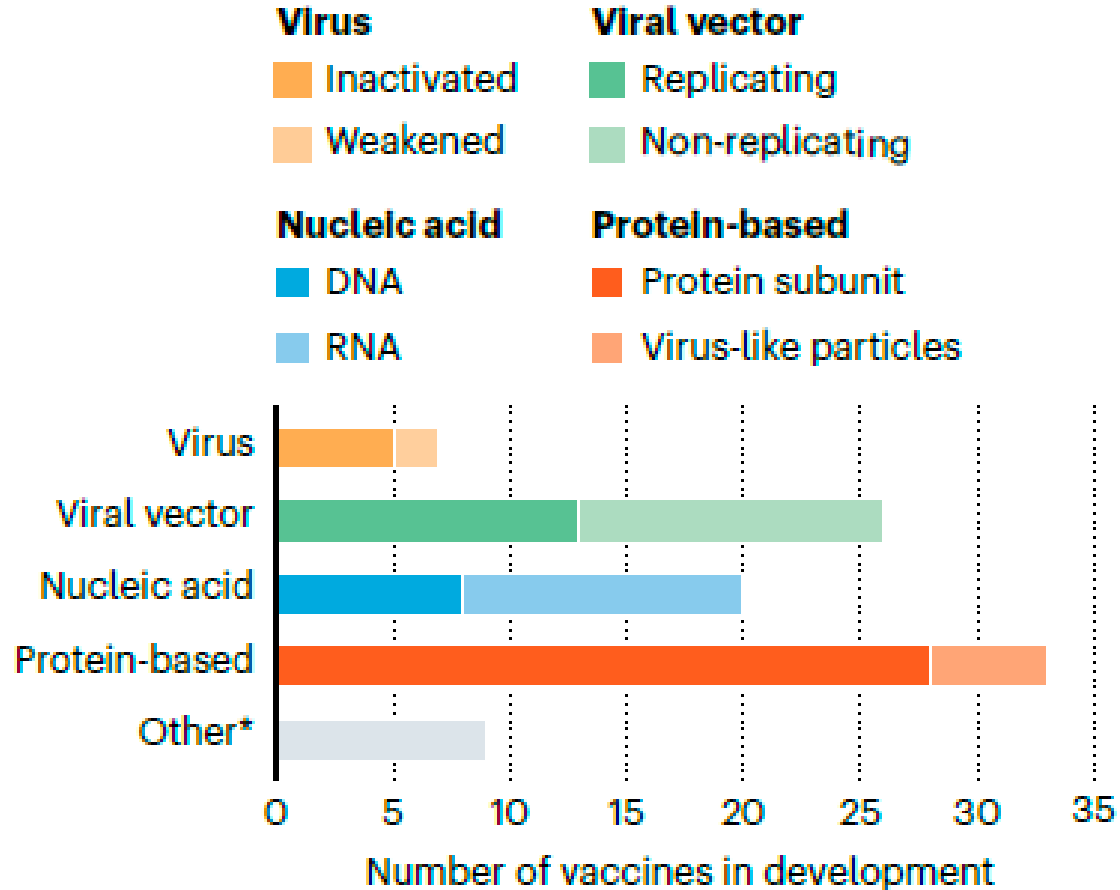
- Primary infection of high risk and severity in those with a weak
immune system that is skewed towards inflammation:
Elderly, Risk groups, Immunodeficient
→ natural immunity is very protective to **97%** and long lasting

Humankind now has
more defenses:
VACCINES: 70-95 % protection



AN ARRAY OF VACCINES

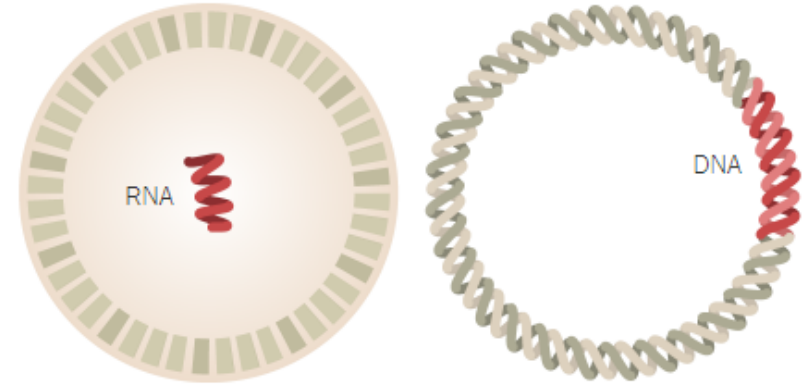
All vaccines aim to expose the body to an antigen that won't cause disease, but will provoke an immune response that can block or kill the virus if a person becomes infected. There are at least eight types being tried against the coronavirus, and they rely on different viruses or viral parts.



* Other efforts include testing whether existing vaccines against poliovirus or tuberculosis could help to fight SARS-CoV-2 by eliciting a general immune response (rather than specific adaptive immunity), or whether certain immune cells could be genetically modified to target the virus.

Genetic Vaccines

Vaccines that deliver one or more of the coronavirus's own genes into our cells to provoke an immune response.



95 % efficacy

Pfizer / BioNTech



BNT162b2

mRNA that encodes for SARS-CoV-2 spike protein.



Pre-S

Moderna

moderna

mRNA-1273

Synthetic messenger RNA that encodes for SARS-CoV-2 spike protein. Pre-S

95 % efficacy

62-90 % effective, Lancet

U. of Oxford
AstraZeneca



AZD1222

*Chimpanzee Adeno vector
expressing SARS-CoV-2
spike protein.* S



Viral Vector Vaccines

Vaccines that contain viruses engineered to carry coronavirus genes. Some viral vector vaccines enter cells and cause them to make viral proteins. Other viral vectors slowly replicate, carrying coronavirus proteins on their surface.

CanSino Biologics



Ad5-nCoV

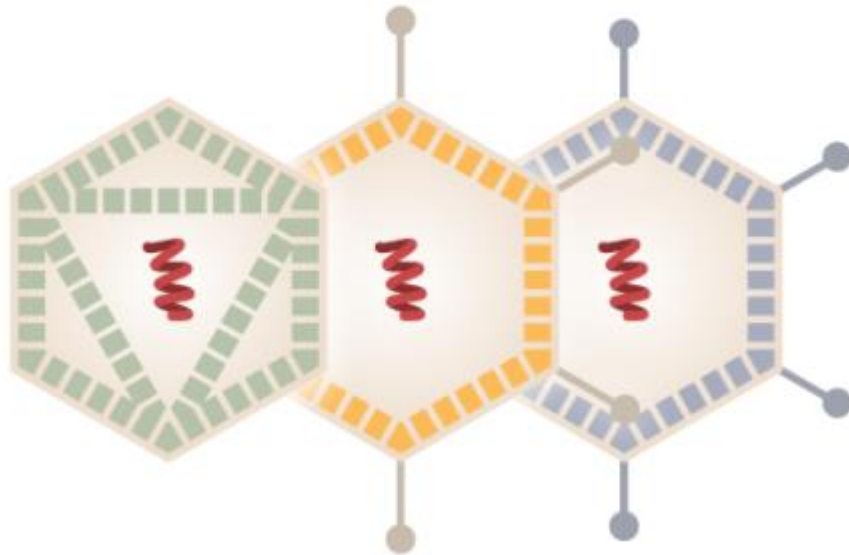
*Ad5 vector expressing
SARS-CoV-2 spike
glycoprotein.*



МИНИСТЕРСТВО
ЗДРАВООХРАНЕНИЯ
РОССИЙСКОЙ ФЕДЕРАЦИИ

92 % effective, Lancet

VACCINE NAME: Sputnik 5 (formerly Gam-Covid-Vac)



J&J

Johnson & Johnson

JNJ-78436735

*Ad26 vector expressing
SARS-CoV-2 spike protein.*

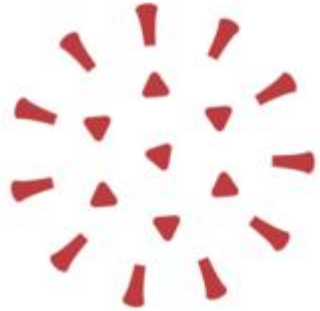
Pre-S



72 % effective

Protein-Based Vaccines

Vaccines that contain coronavirus proteins but no genetic material. Some vaccines contain whole proteins, and some contain fragments of them. Some pack many of these molecules on nanoparticles.

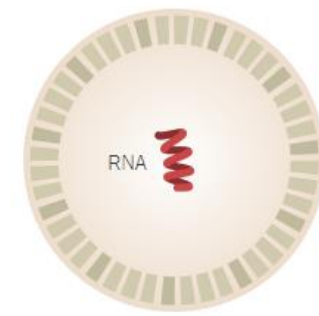


NOVAVAX

SARS-CoV-2 spike protein.

14/06/21: **90 % efficacy**
(100 % death/hospital)

- 93% efficacy against predominantly circulating Variants
- 91% efficacy in high-risk populations
- All COVID-19 hospitalizations/death occurred in the placebo group



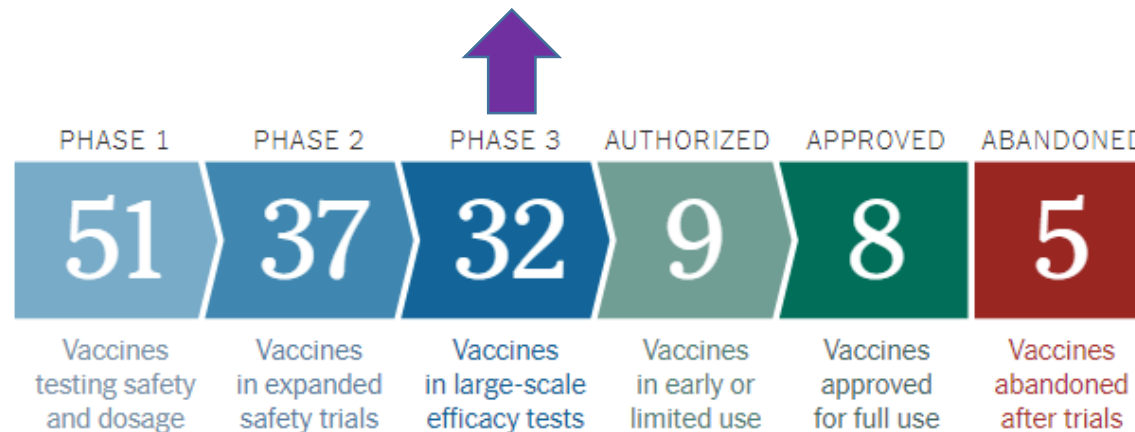
UREVAC

mRNA-

VACCINE NAME: CVnCoV

16/06/21: **48 % efficacy**
(100 % death/hospital)

- Too low dose? 12 μg vs 30-100 μg





A vaccine

is a **medicine**

SAFE and **EFFICACIOUS**

that has **components of a microorganism**

that stimulate the immune system to build **immune MEMORY**

that is efficacious to **prevent infectious diseases**

Vaccines are safe



Safety results
Extremely rare adverse events, such as 1 in 100,000

AstraZeneca (Vaxzevria) vaccine

Platelets decrease + unusual blood clots

~1 case in 100,000 vaccinees with one dose (316 in 36 millions in EU, 28/05)
8 times less after 2nd dose (10 million, in United Kingdom, 19/05)
Severity has decreased because of awareness and early treatment
Middle age adults

Pfizer, Moderna, AstraZeneca, Janssen vaccines are SAFE

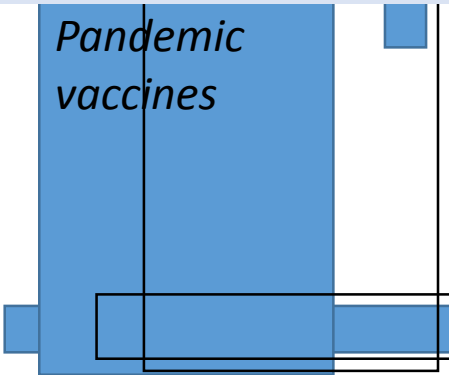
after approval

Comirnaty (Pfizer) and Spikevax (Moderna) vaccines

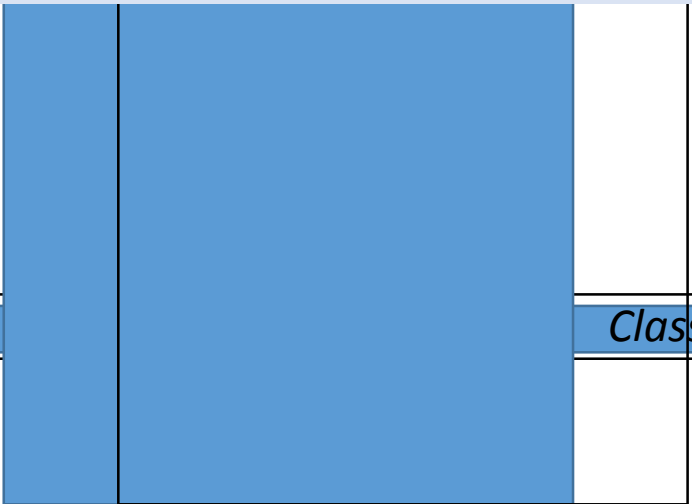
Severe anafilaxis

~1 case in 100,000 vaccinees
Severity is controlled because of awareness and early treatment

Adverse effects: first 6 weeks after 2nd dose in each vaccinated person



Pandemic vaccines



Classical vaccines

months

years...



Safety results



Safety results



A vaccine

is a **medicine**

SAFE and **EFFICACIOUS**

that has **components of a microorganism**

that stimulate the immune system to build **immune MEMORY**

that is efficacious to **prevent infectious diseases**

That prevents

- Asymptomatic infection

There is **NO** protection from infection, only a **2-fold decrease (with Delta variant)**

- Mild symptoms
- Severe symptoms
- death



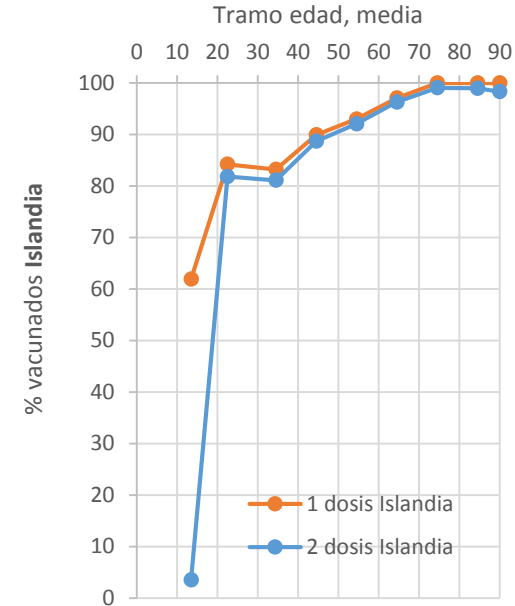
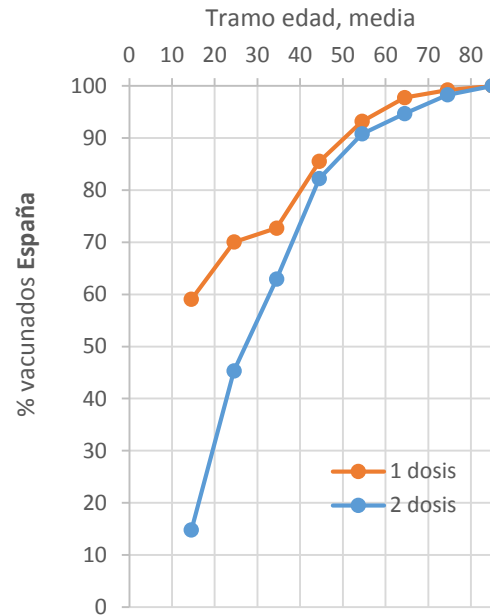
anti covid-19 vaccines: they protect from disease

- Virus transmission and spread (confer herd immunity)

¿NO? (viral load in vaccinees is almost the same)

Pandemic-controlling vaccines: those that would also protect from transmission

Vaccination campaigns have to be very comprehensive in order to protect all at-risk



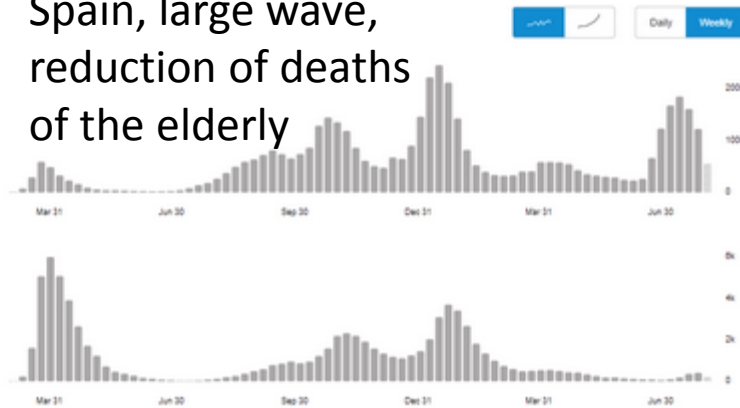
Spain Situation

4,677,883
confirmed cases

82,407
deaths

Source: World Health Organization
Data may be incomplete for the current day or week.

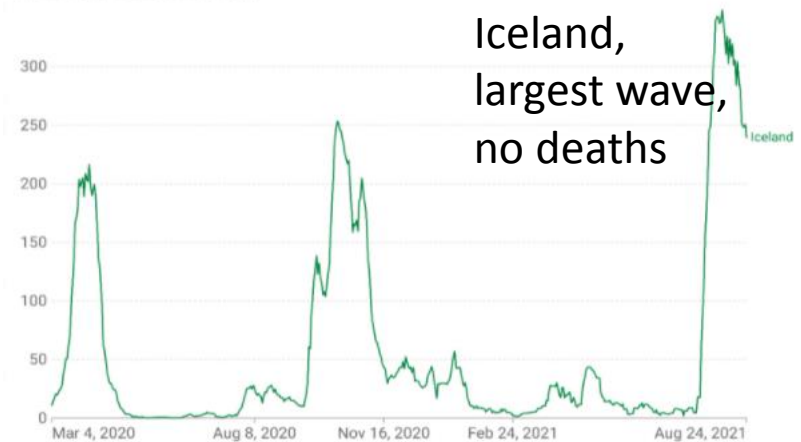
Spain, large wave, reduction of deaths of the elderly



Daily new confirmed COVID-19 cases per million people

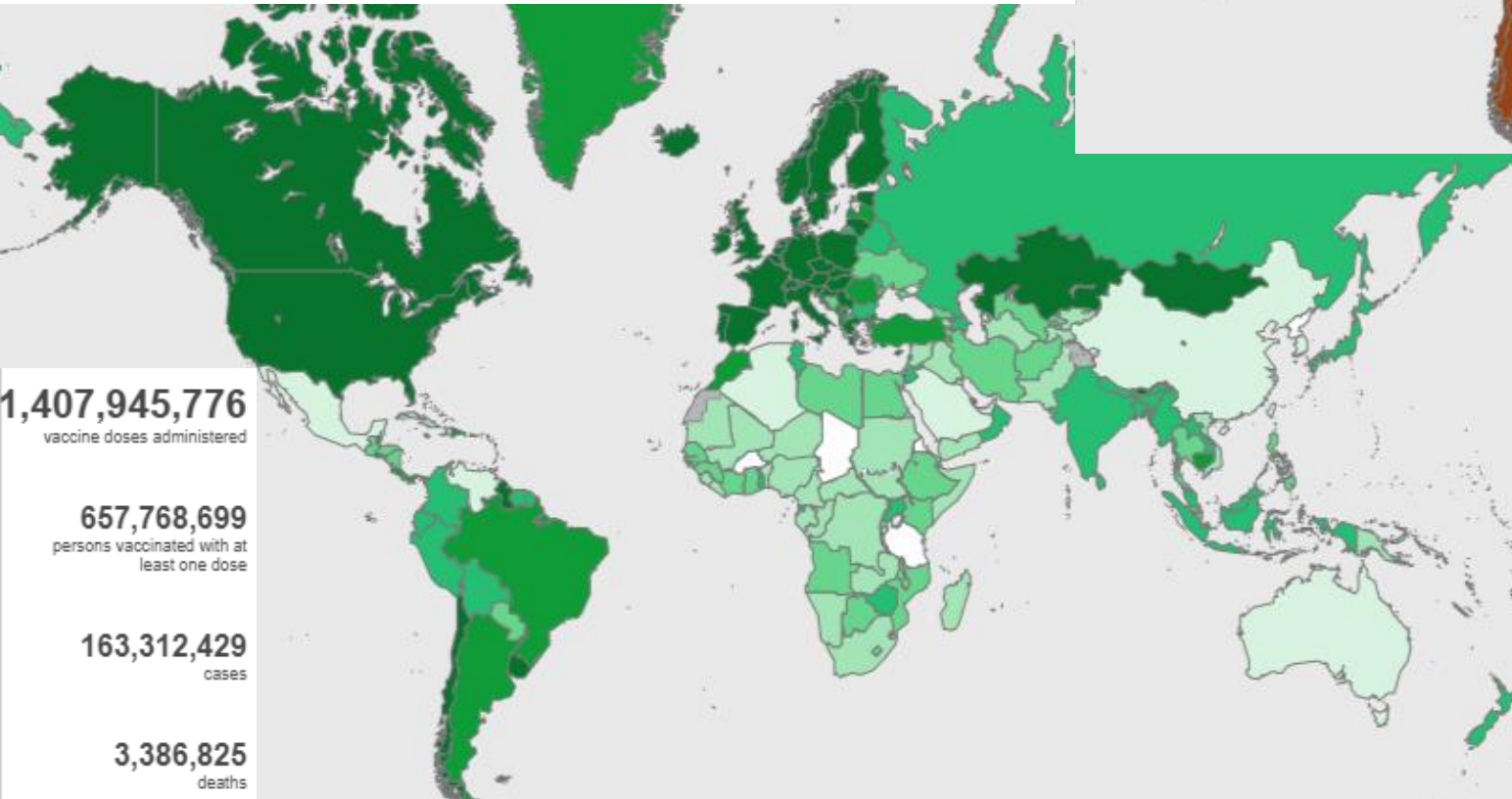
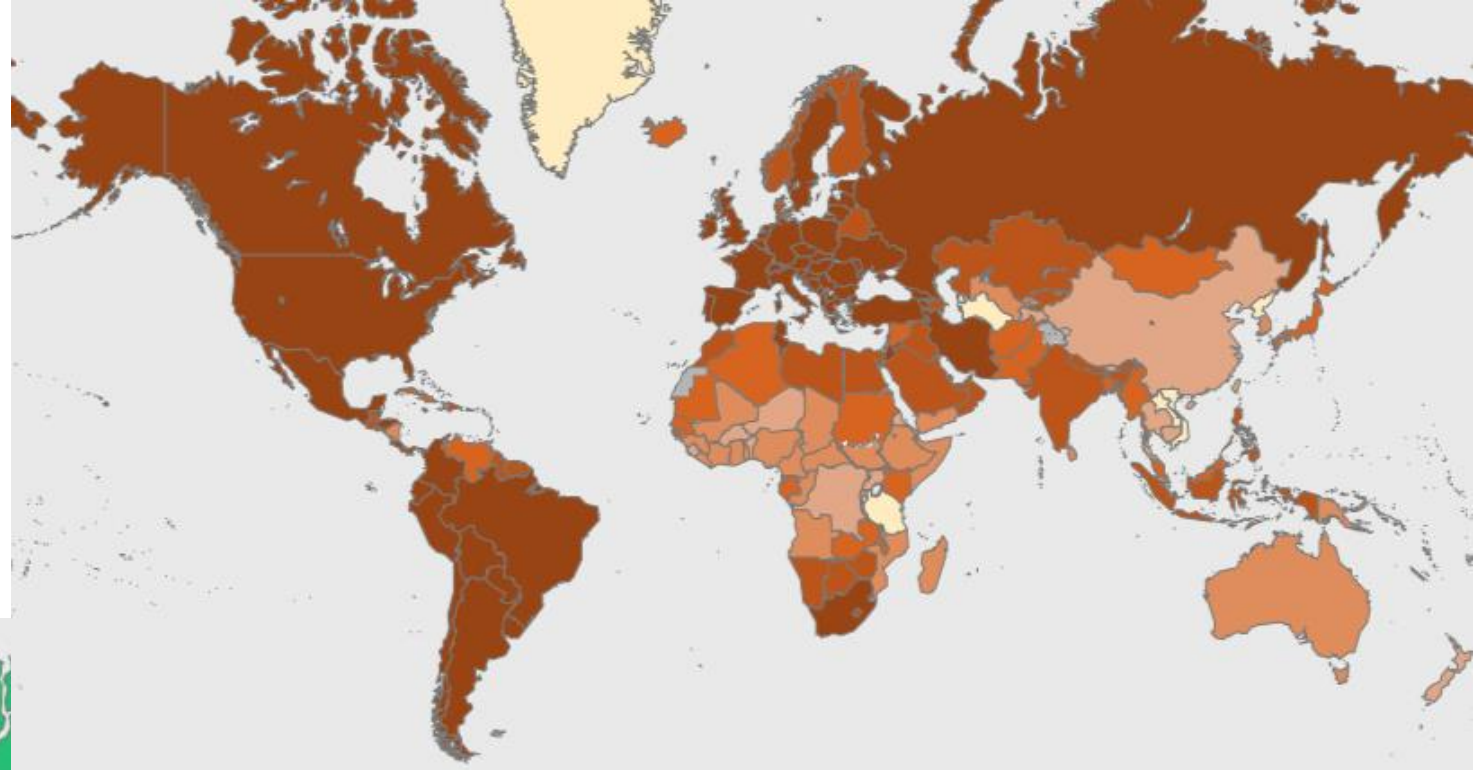
Shown is the rolling 7-day average. The number of confirmed cases is lower than the number of actual cases; the main reason for that is limited testing.

Our World in Data



Iceland, largest wave, no deaths

Deaths per
100.000 inhabitants



Persons **vaccinated**
with at least one dose
per 100 inhabitants

Unequal distribution
of vaccine doses
around the world



COVID-19

< BACK TO OUR ALLIANCE

AS PART OF ITS MISSION TO SAVE LIVES, REDUCE POVERTY AND PROTECT THE WORLD AGAINST THE THREAT OF EPIDEMICS, GAVI HAS HELPED VACCINATE MORE THAN 822 MILLION CHILDREN IN THE WORLD'S POOREST COUNTRIES, PREVENTING MORE THAN 14 MILLION FUTURE DEATHS

Gavi, the Vaccine Alliance, helps vaccinate almost half the world's children against deadly and debilitating infectious diseases



GAVI, THE VACCINE ALLIANCE

PREMIO PRINCESA DE ASTURIAS DE COOPERACIÓN INTERNACIONAL 2020



When the pandemic strikes, no-one is safe until everyone is safe



Independent Panel for WHO Evaluation:

3 immediate actions:

1. High income countries: supply **COVAX** with:
1,000 million **doses** by 1st September 2021
and 2,000 million doses by mid 2022.

2. High income countries and pharmaceutical companies producing vaccines:
voluntary licensing of **patents and technology transfer**.
If not in few months: compulsory.

3. Immediate commitment to supply in 2021
60% of promised **19,000 million** to the Accelerator **Access to COVID-19 Tools (ACT)**.

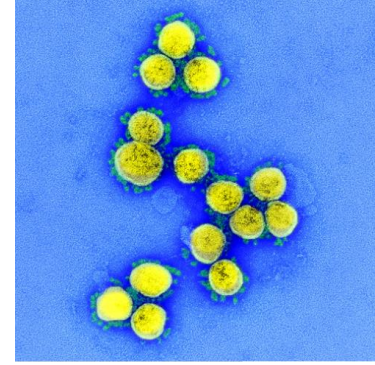
Report of the Independent Panel for Pandemic Preparedness and Response:
making COVID-19 the last pandemic. Ellen Johnson Sirleaf, Helen Clark.
[https://doi.org/10.1016/S0140-6736\(21\)01095-3](https://doi.org/10.1016/S0140-6736(21)01095-3)

Minimal Goal in vaccination:
Health care professionals (3% population)
Goal: 20% population by the end of 2021

India stopped supplying COVAX its vaccines
during its severe wave: up to 190 million
doses were held for Indians



28 August 2021



Hay algo
que da más miedo
que las vacunas



No tenerlas

- **We will all get infected**, hopefully once we are safely vaccinated
- **Variants evolve to be more transmissible**, not to escape immunity
- **With 15-20% of risk groups not vaccinated, new waves still as serious as before**
- **Infection after vaccination is usually safer** (but for immuno-compromised) and will each time **reinforce immune memory**
- Vaccines only protect the person who is vaccinated. **Non-vaccinated people have the same risk of severity as always**, and are now more exposed to silent transmitters.
- Vaccines are **efficacious and safe**
- Vaccines **MUST reach the whole planet**
- *What is the risk of long-COVID among young low-risk groups?*



Hay algo
que da más miedo
que las vacunas



No tenerlas

- **Nos infectaremos todos**, mejor que nos pille vacunados.
- Variantes mas **transmisibles**, no que se escapen
- Aprox la **mitad de la población todavía sin inmunidad**, aunque ya casi no son de grupos de alto riesgo
- La **infección después de la vacunación no tiene casi riesgo**, aunque reforzará y ampliará nuestra memoria inmunitaria
- La vacuna solo protege al vacunado; **los no vacunados siguen teniendo el mismo riesgo que antes**, pero con más contagiosos silenciosos.
- Vacunas **eficaces y seguras**
- Vacunar a todo el **planeta**
- *¿Qué riesgo y secuelas tienen qué jóvenes?*

Mutaciones del coronavirus SARS-CoV-2

Los coronavirus **mutan poco**, 10 veces menos que la gripe, porque corrigen sus errores y no recombinan (la gripe sí)
pero en los grandes brotes se imponen rápidamente algunas nuevas mutaciones

Replicación masiva mundial, grandes brotes →

se imponen algunas **variantes**:

España, Julio-Agosto 2020

Reino Unido, B.1.1.7

Sudáfrica, B.1.351

Brasil, P.1

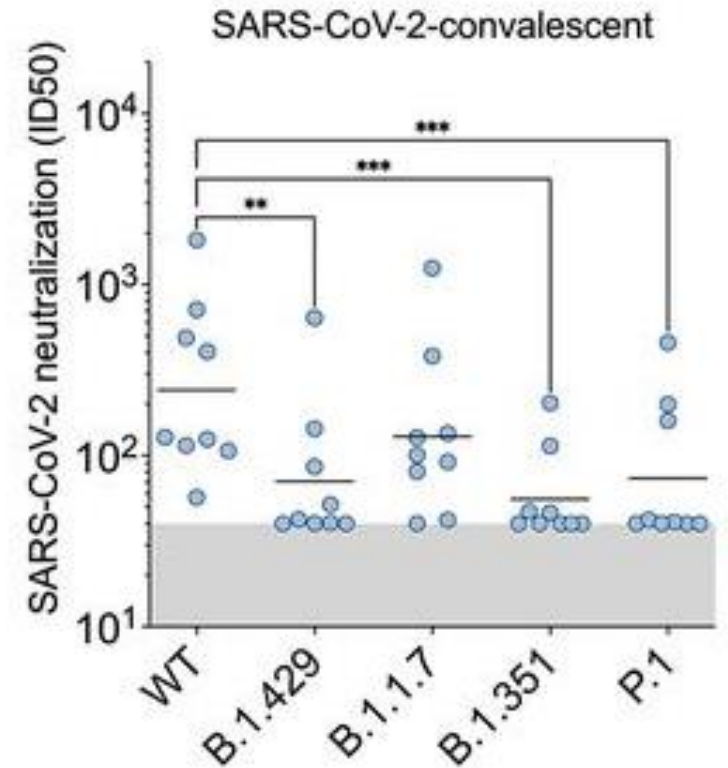
California, CAL.20C (B.1.427/B.1.429)

Los coronavirus de animales y humanos no tienen serotipos;
nunca han logrado escapar de la respuesta de anticuerpos.

La viruela, la polio, el sarampión **tampoco** – a pesar de replicación masiva mundial y vacunación masiva mundial.

Gripe A **sí se escapa**. Gripe B **básicamente no**.

neutralizing
titers reduced
2-3.5 fold



McCallum et al. SARS-CoV-2 immune evasion by the B.1.427/B.1.429 variant of concern
Science 01 Jul 2021 DOI: 10.1126/science.abi7994