I vaccini e le nuove tecnologie

Mariagrazia Pizza

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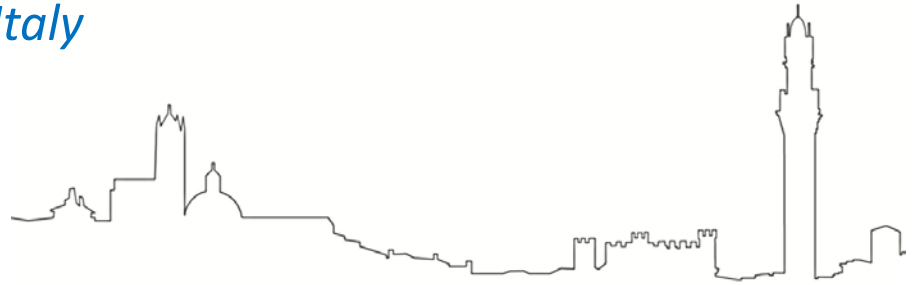
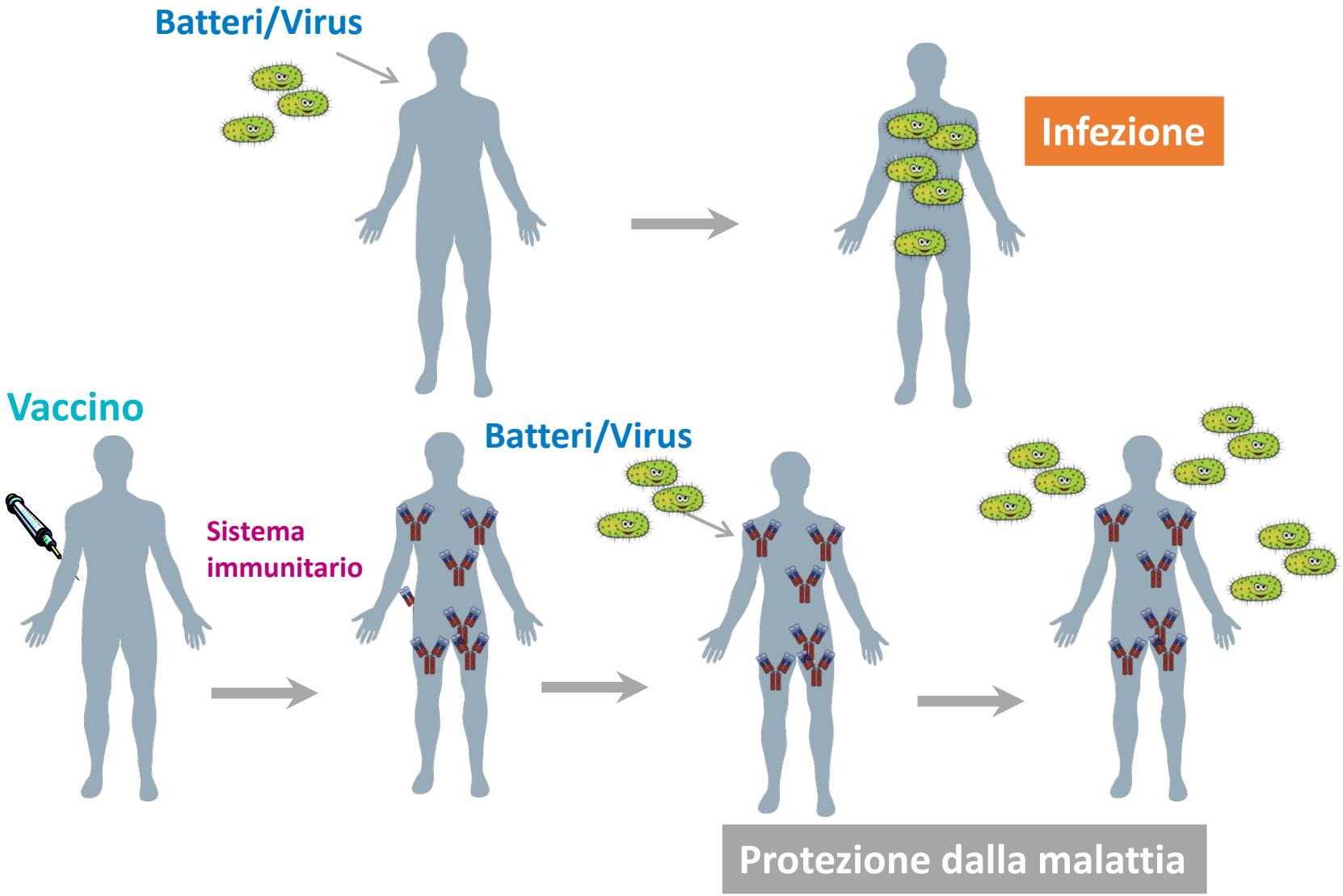
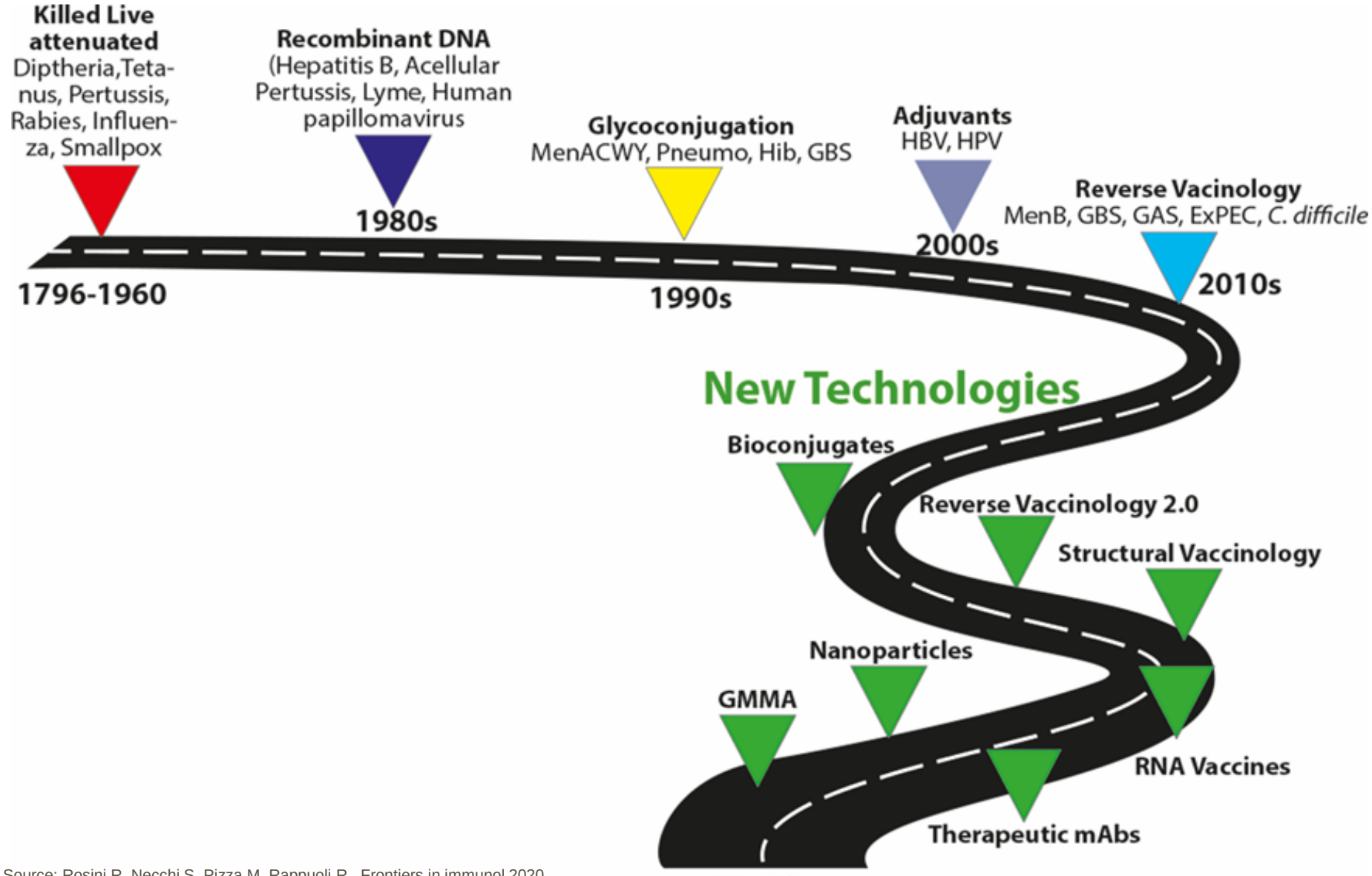
5 Marzo 2021



Cosa è un vaccino e come funziona?

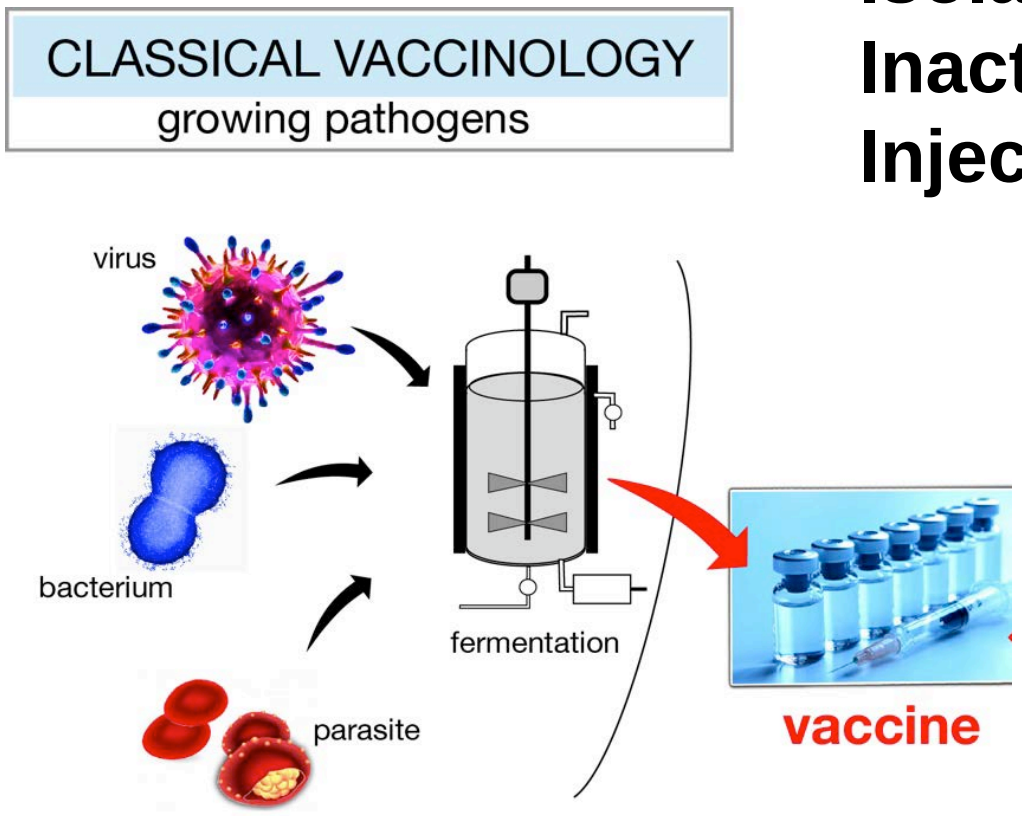


New technologies led to the development of new vaccines and will allow to conquer new diseases



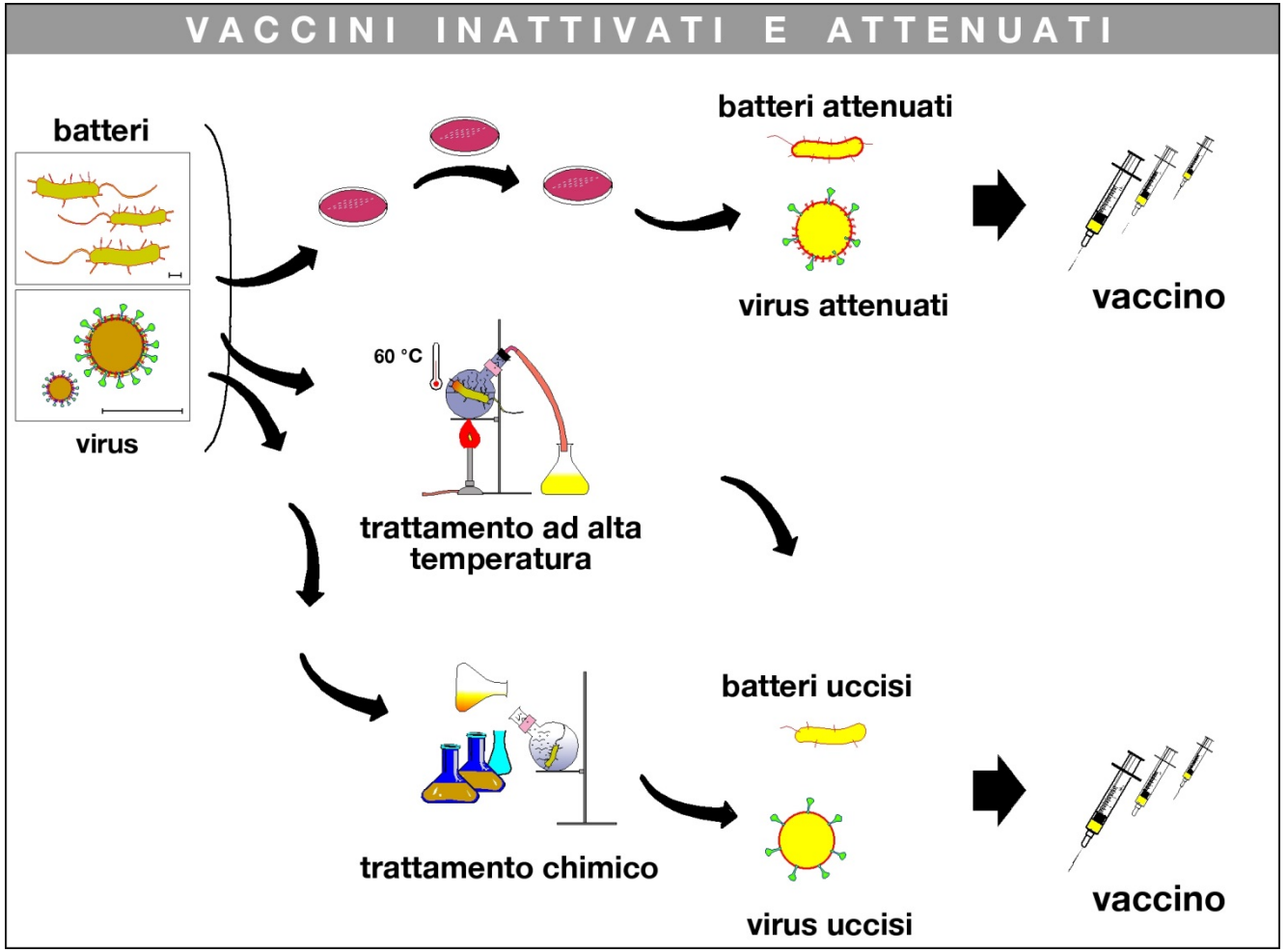
- Source: Rosini R, Necchi S, Pizza M, Rappuoli R.. Frontiers in immunol 2020

From Jenner to Pasteur to Hilleman



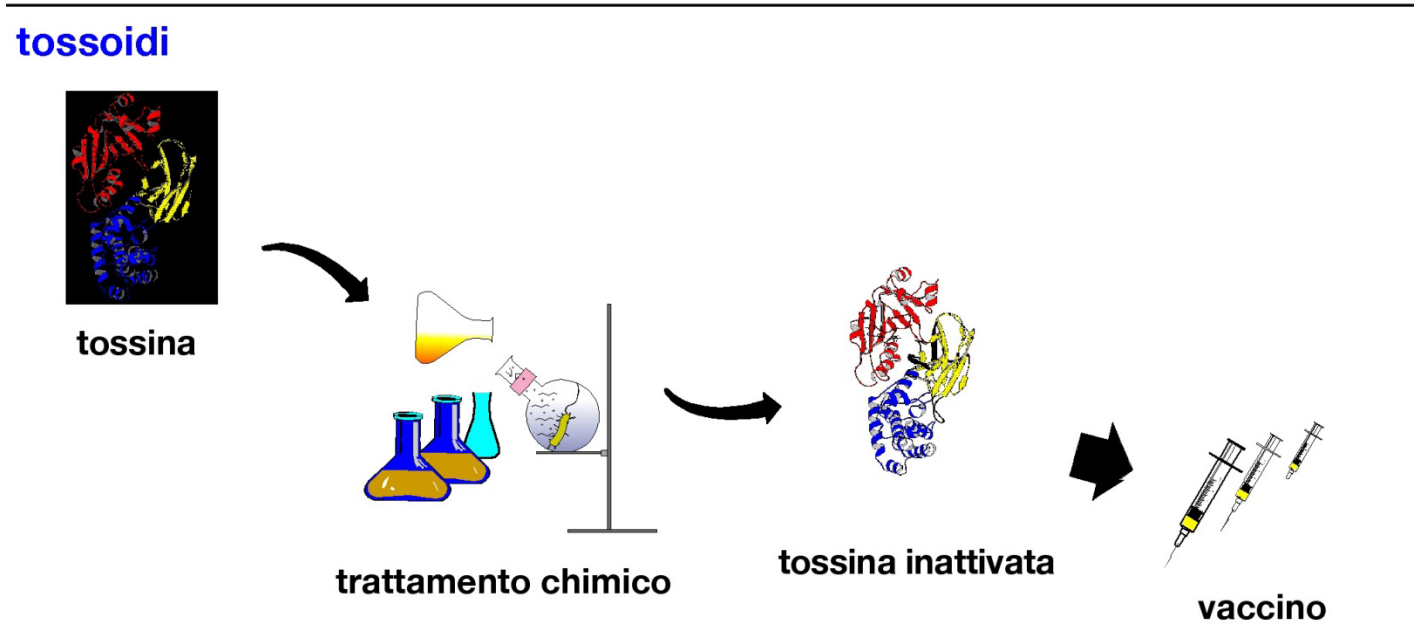
Isolate
Inactivate
Inject the microorganism causing disease

Traditional vaccines



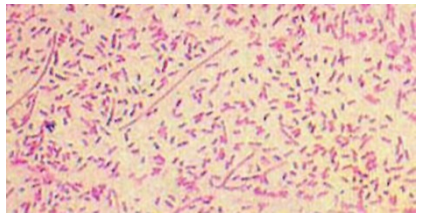
Subunit vaccines based on chemical inactivation

I 1924 Ramon demonstrated that the difteria toxin could be inactivated by chemical treatment. Vaccines against difteria, tetanus and pertussis are all based on this approach

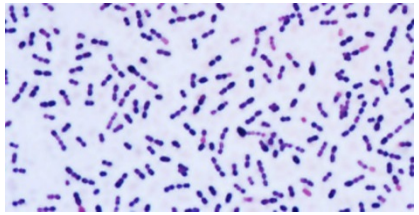


Capsular polysaccharides & Conjugates

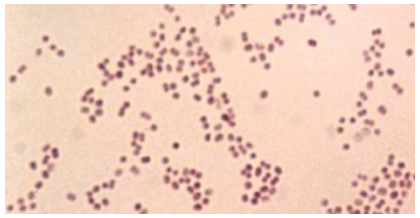
Haemophilus influenzae type B (Hib)



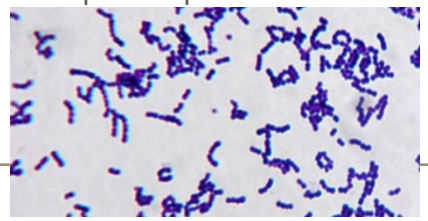
Pneumococcus



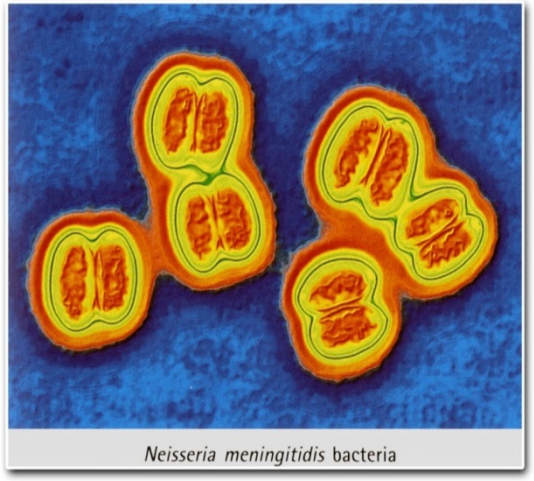
Meningococcus

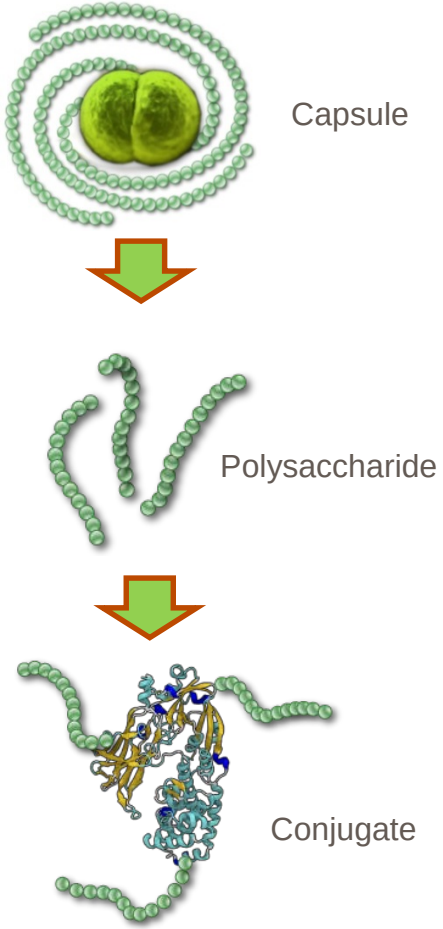


Group B streptococcus

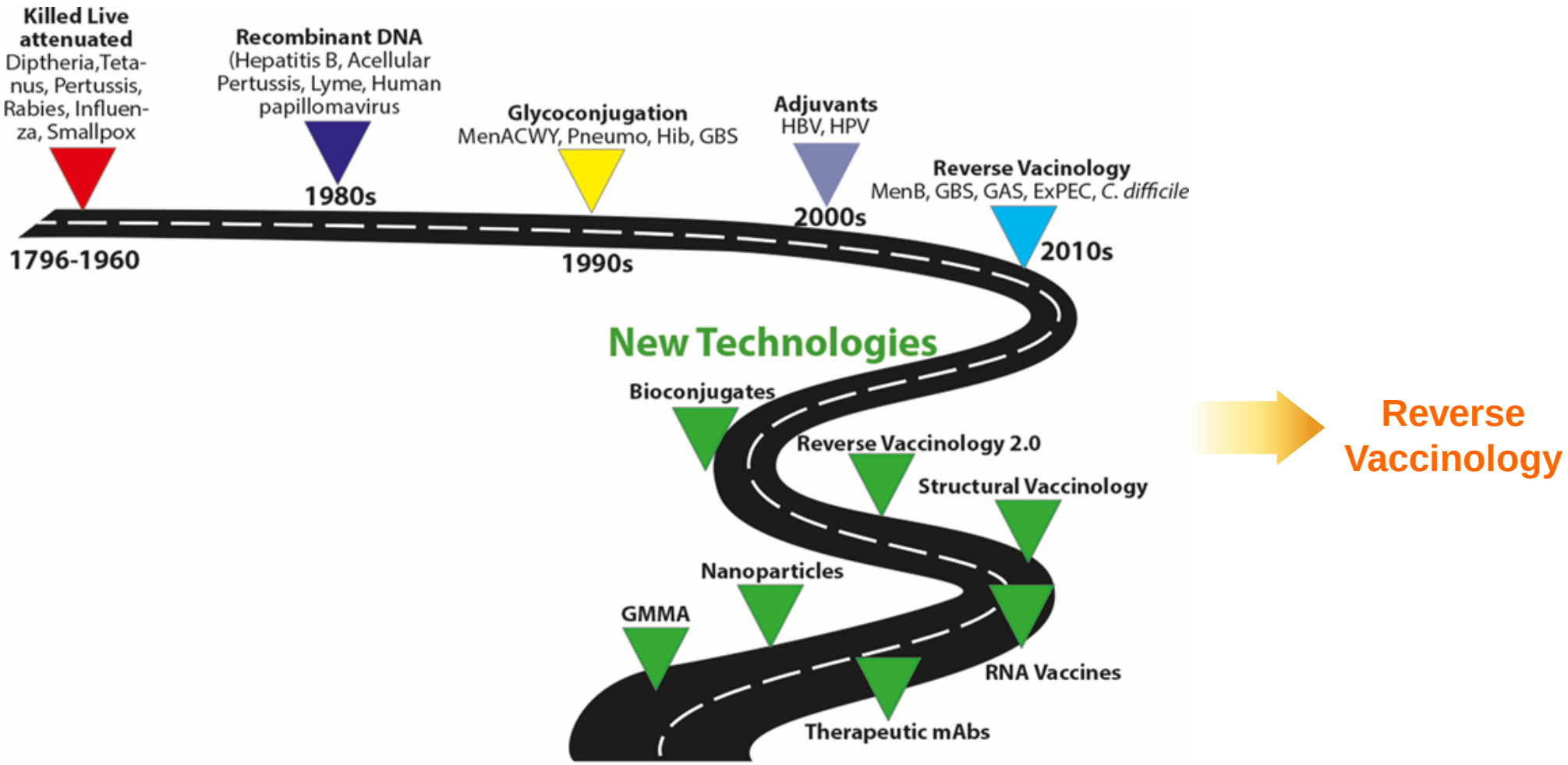


Capsule





New technologies led to the development of new vaccines and will allow to conquer new diseases



- Source: Rosini R, Necchi S, Pizza M, Rappuoli R.. Frontiers in immunol 2020

Meningococcal meningitis
a rare disease but..



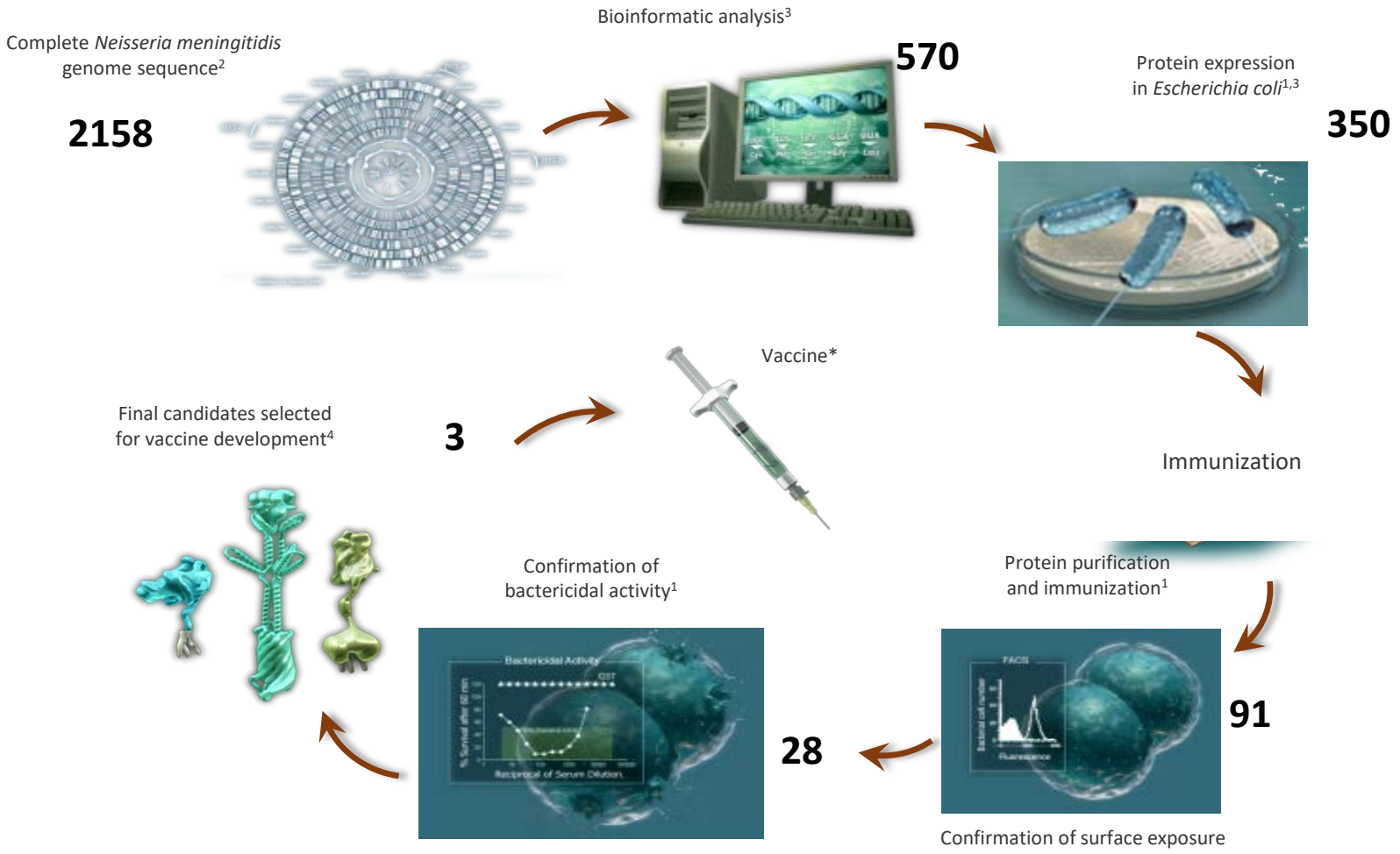

- Infection is very fast, 10-15% die within 48 hours
- 25% of survivors have lifelong sequelae, some are devastating

Source: Anne Geddes pictures

http://protectingourtomorrows.tumblr.com/#post/67657878221/on-her-decision-to-participate-in-protecting-our?&_suid=139224491615201190848382540457

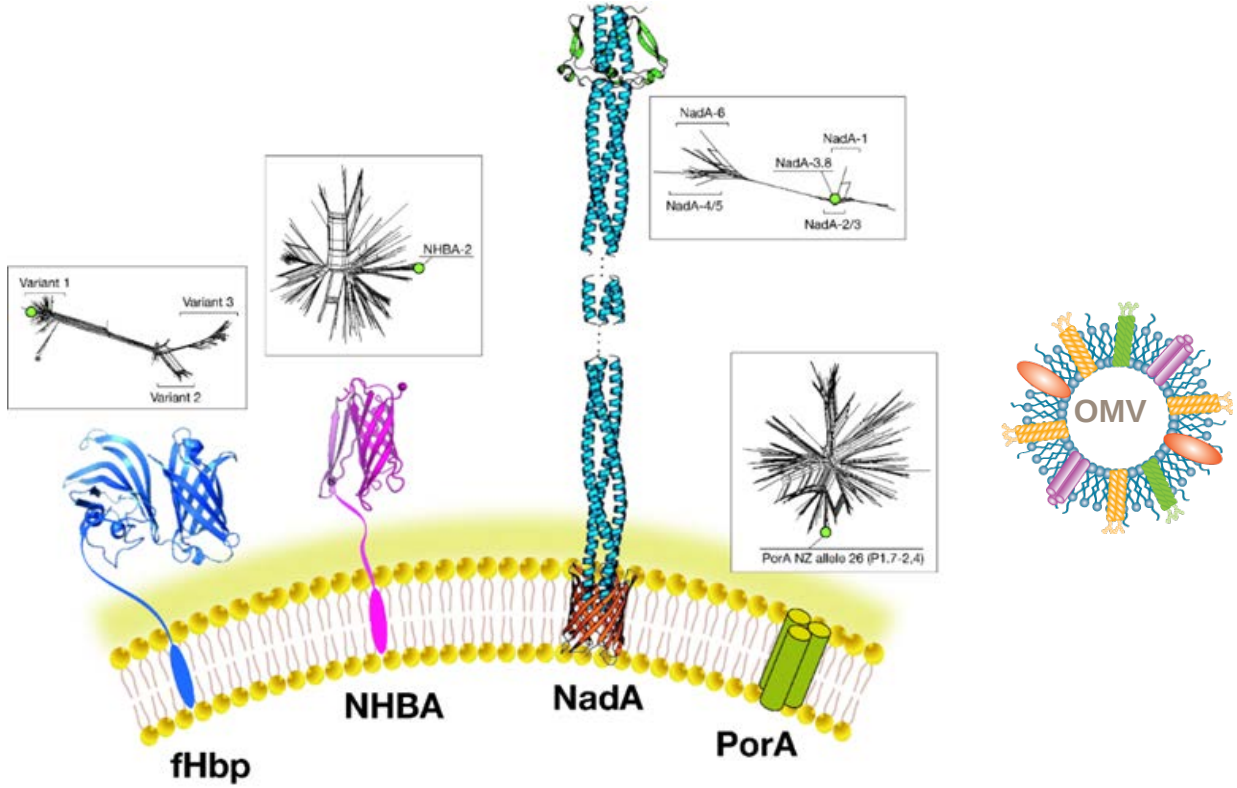
Reverse Vaccinology

A genomic-based approach to vaccine development



2. Tettelin H, et al. *Science*. 2000;287:1809-1815; 3. Pizza M, et al. *Science*. 2000;287:1816-1820; 4. Giuliani M, et al. *PNAS*. 2006;103:10834-10839; 5. Donnelly J, et al. *Proc Natl Acad Sci U S A*. 2010;107:19490-19495; Images are ©Hurd Studios, 2011 and 2012.

4C MenB Vaccine

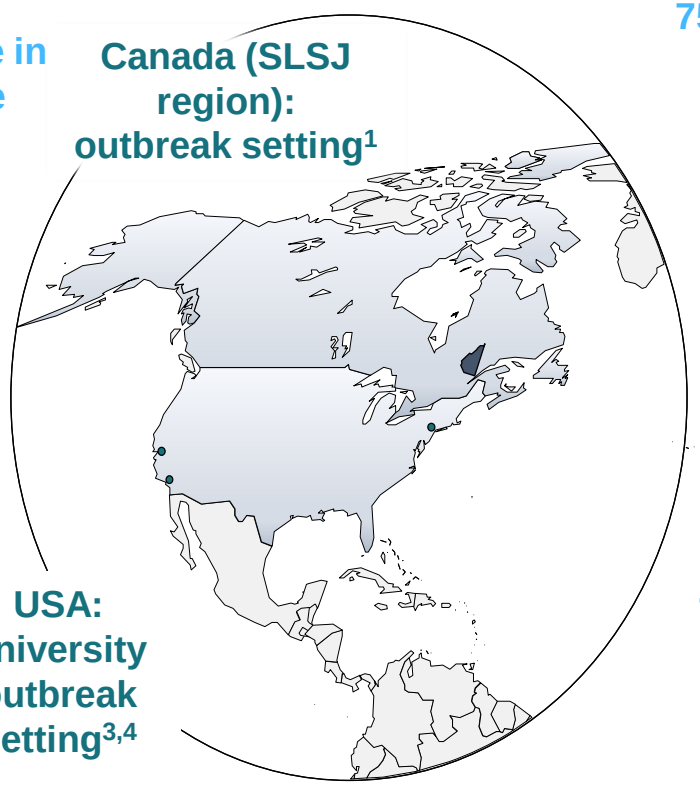


Masignani, V. et al. 2019 Front Immunol

4CMenB is supported by data from real-world experience across multiple settings

96% decrease in MenB disease

Canada (SLSJ region): outbreak setting[1]

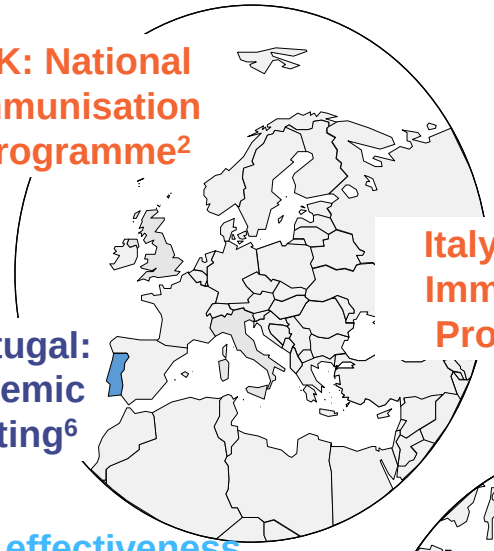


USA: university outbreak setting[3,4]

No cases in vaccinated individuals

75% decrease in MenB disease

UK: National Immunisation Programme[2]



Portugal: endemic setting[6]

79% effectiveness

Italy: National Immunisation Programme[7]

Effectiveness of 91% in Veneto and 93,6 in Tuscany

South Australia: State-wide study in adolescents[5]

No cases in vaccinated individuals

Clinical development > Objectives & Characteristics

Phase 1:

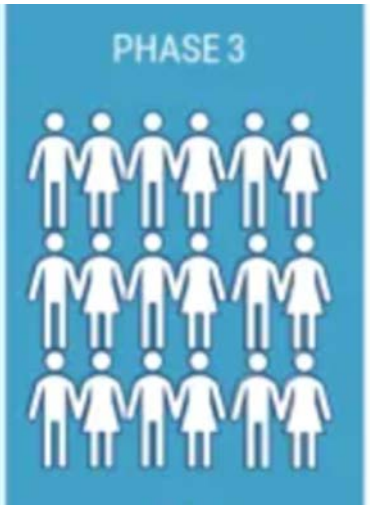
- To select a vaccine dose that is **safe** and **suficiently well-tolerated** to justify exposure to larger study populations in Phase 2
- About 50 subjects

Phase 2:

- **Dose selection, immunogenicity endpoints, safety evaluation**
- Several hundred subjects

Phase 3

- Define protection in a population that is likely to experience the disease. Large safety data. Define correlates of protection
- Enroll several thousand subjects

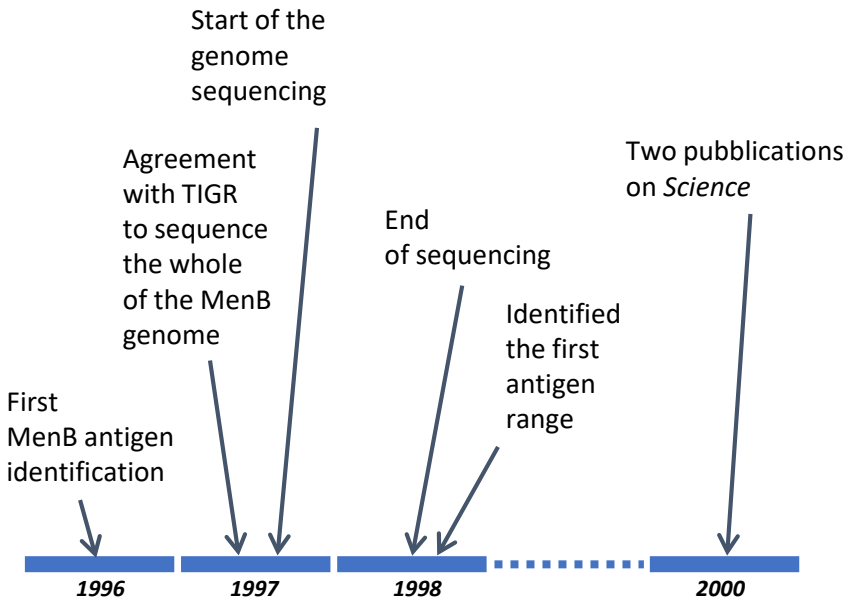


20 milioni fase 1

70-100 milioni fase 2

700 milioni fase 3 + impianto

The development steps of MenB vaccine



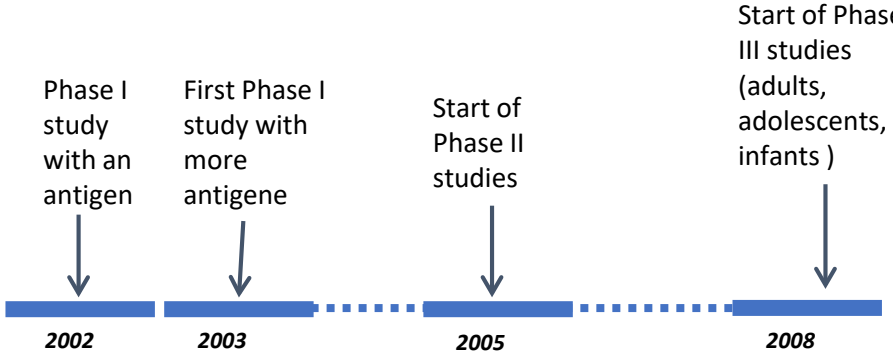
Research:

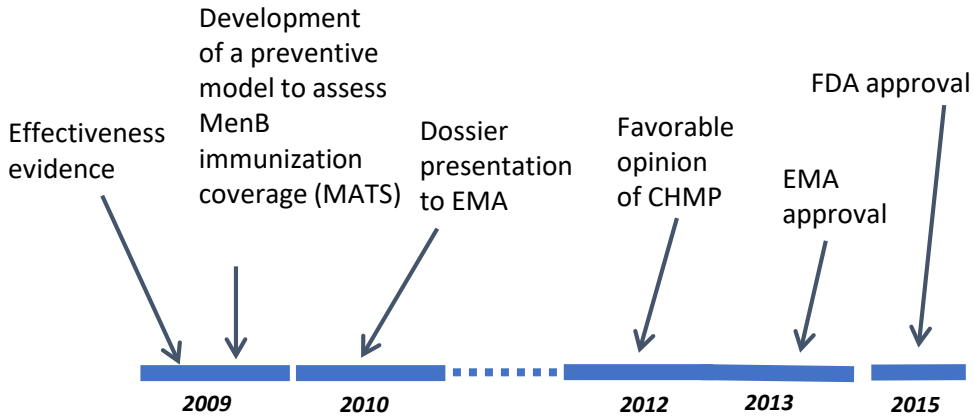
→ 6 months for the complete genome

→ 12 to identify protective antigens, never previously discovered by traditional approaches

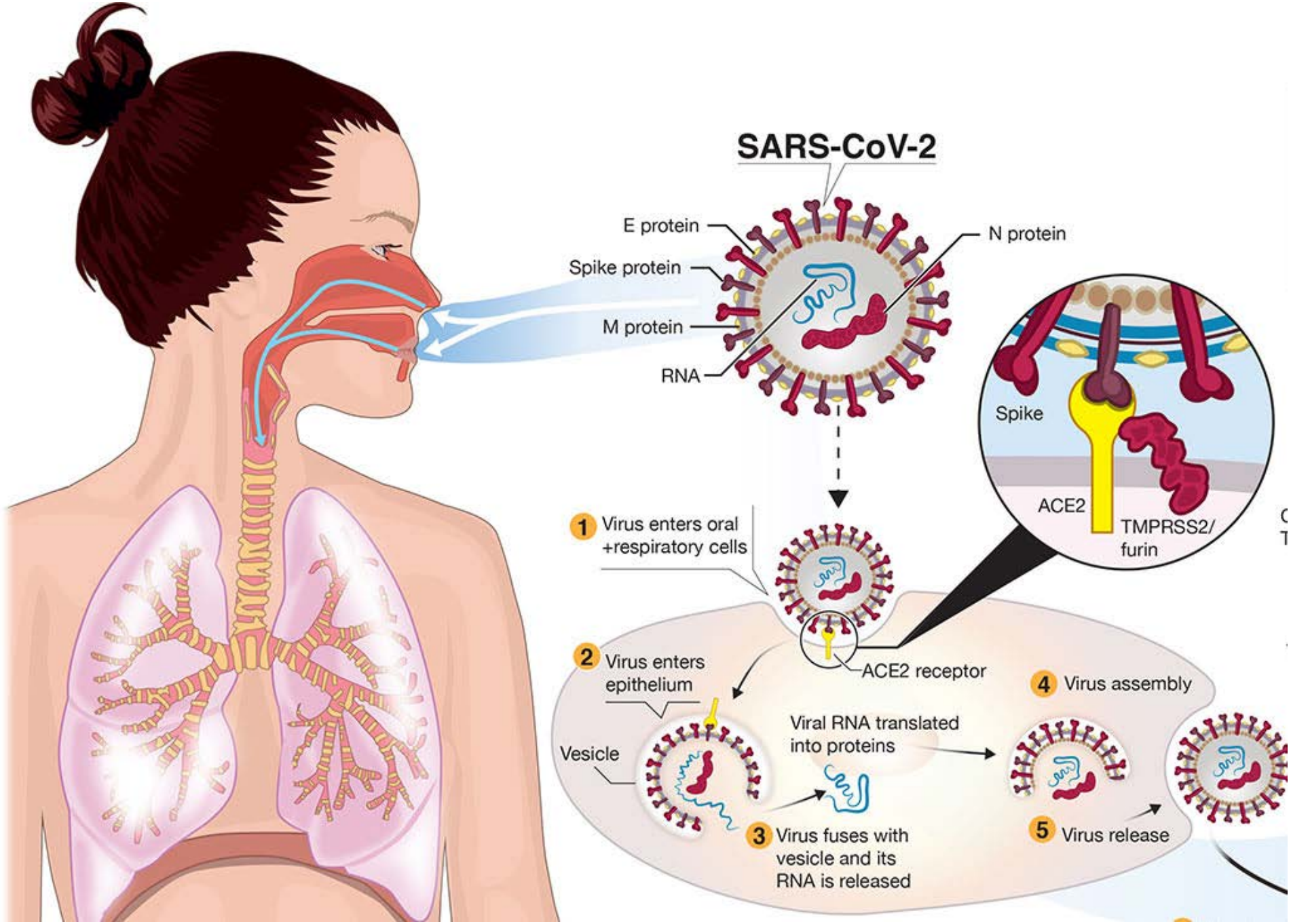
Clinical Development:

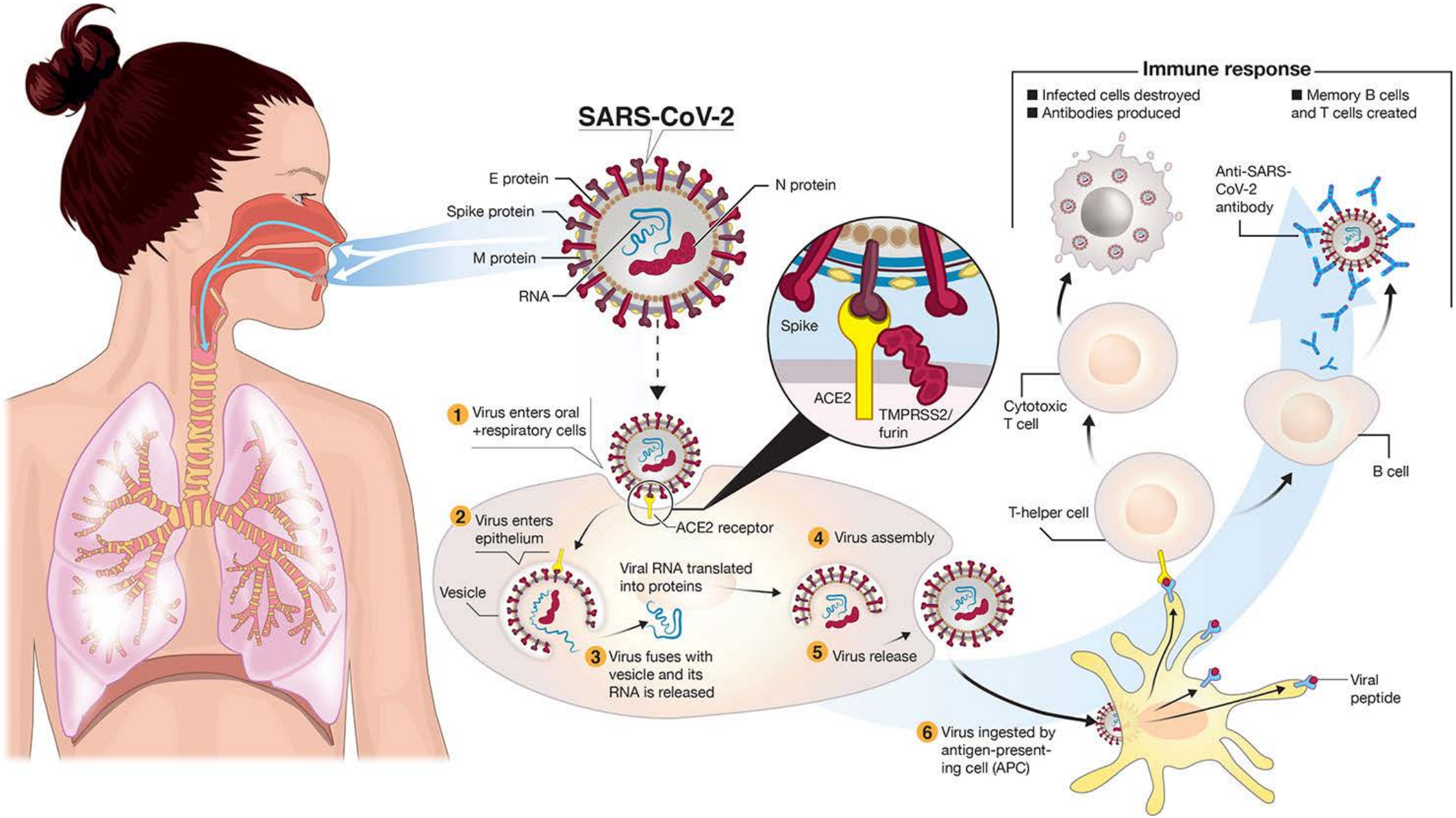
→ 9 years to complete the dossier including infants, children, adolescents and adults





*The Institute for Genomic Research, Publications sciences : Tettelin H et al, Science 287 1809-1815, 2000; Pizza M et al, Science 287: 1816-1820, 2000


SARS-CoV-2
E protein
Spike protein
M protein
RNA
N protein
Spike
ACE2
TMPRSS2/
furin
1 Virus enters oral
+respiratory cells
ACE2 receptor
2 Virus enters
epithelium
Vesicle
Viral RNA translated
into proteins
3 Virus fuses with
vesicle and its
RNA is released
4 Virus assembly
5 Virus release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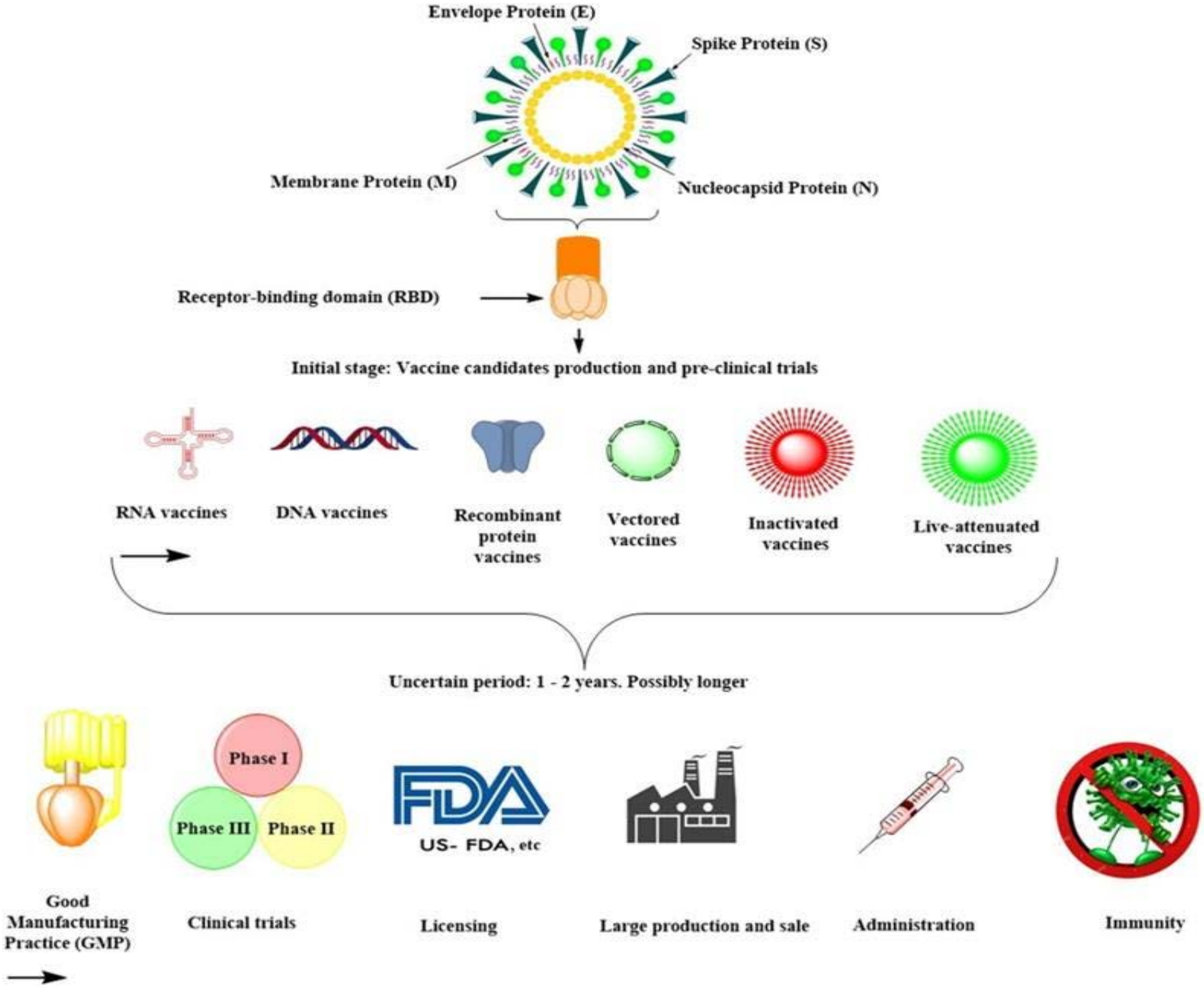
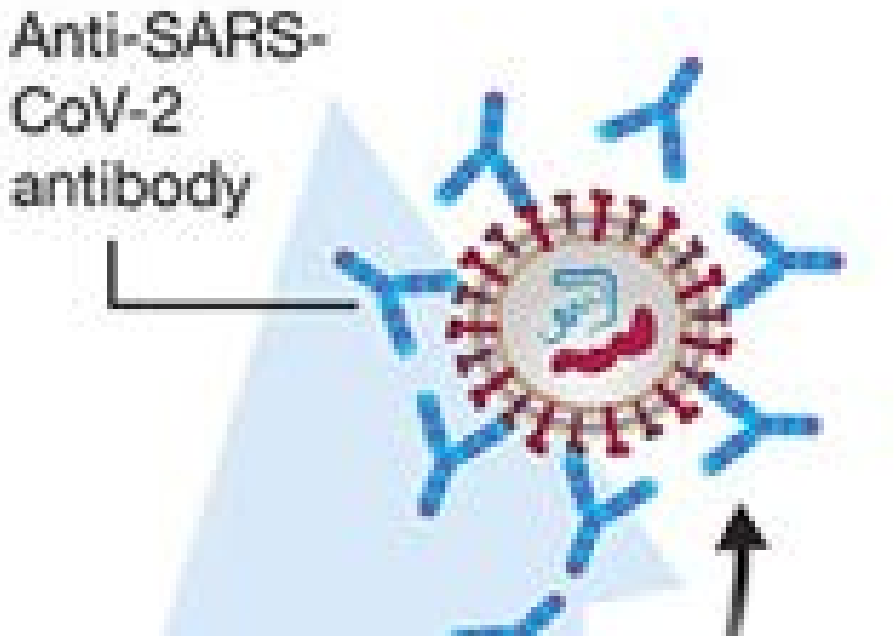
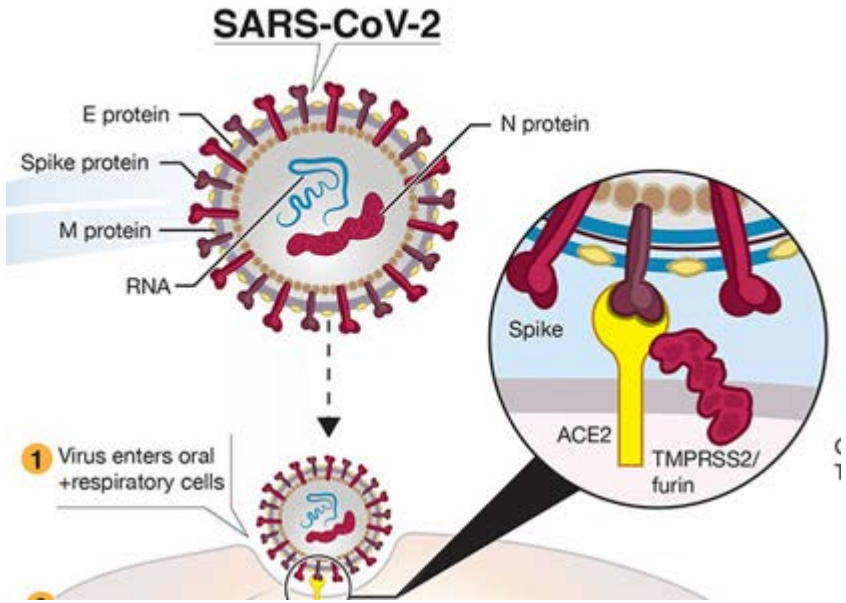
2 Virus enters
epithelium
ACE2 receptor
Vesicle
Viral RNA translated
into proteins
3 Virus fuses with
vesicle and its
RNA is released
4 Virus assembly
5 Virus release
6 Virus ingested by
antigen-present-
ing cell (APC)
Viral
peptide
Immune response
Infected cells destroyed
Antibodies produced
Memory B cells
and T cells created
Anti-SARS-
CoV-2
antibody
Cytotoxic
T cell
T-helper cell
B cell


Envelope Protein (E)
Spike Protein (S)
Membrane Protein (M)
Nucleocapsid Protein (N)
Receptor-binding domain (RBD)
Initial stage: Vaccine candidates production and pre-clinical trials
RNA vaccines
DNA vaccines
Recombinant protein vaccines
Vectored vaccines
Inactivated vaccines
Live-attenuated vaccines
Uncertain period: 1 - 2 years. Possibly longer
Phase I
Phase III
Phase II
FDA
US- FDA, etc
Good Manufacturing Practice (GMP)
Clinical trials
Licensing
Large production and sale
Administration
Immunity


Anti-SARS-CoV-2 antibody


SARS-CoV-2
E protein
Spike protein
M protein
RNA
N protein
Spike
ACE2
TMPRSS2/
furin
1 Virus enters oral
+respiratory cells

Old technologies for the development of COVID vaccines

Killed Live attenuated
Diptheria,Tetanus, Pertussis, Rabies, Influenza, Smallpox

Recombinant DNA
(Hepatitis B, Acellular Pertussis, Lyme, Human papillomavirus

Glycoconjugation
MenACWY, Pneumo, Hib, GBS

Adjuvants
HBV, HPV

Reverse Vacinology
MenB, GBS, GAS, ExPEC, *C. difficile*

1796-1960

1980s

1990s

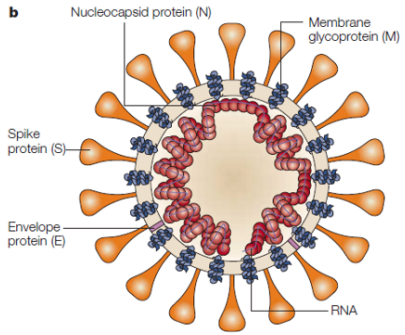
2000s

2010s

New Technologies

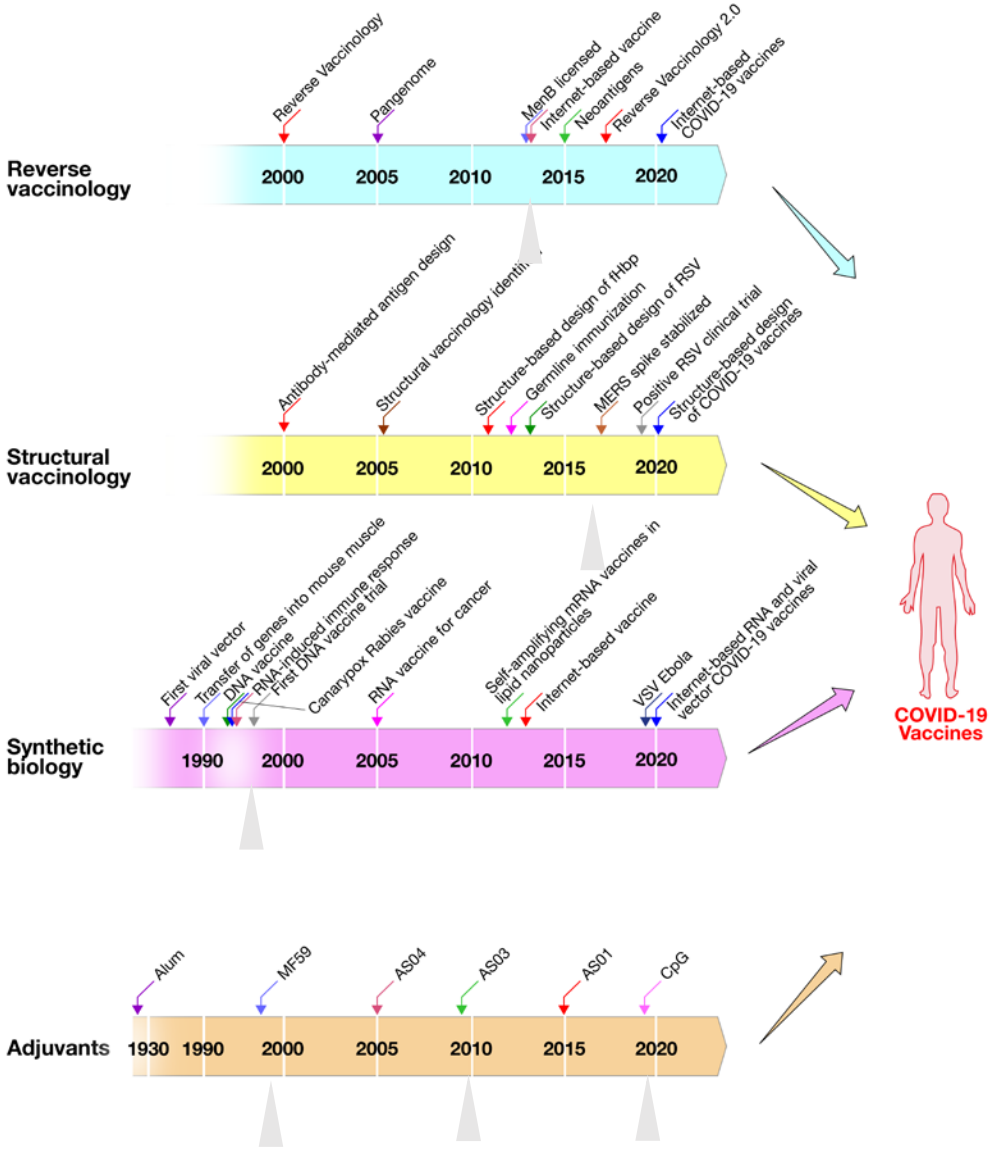
- Bioconjugates
- Reverse Vaccinology 2.0
- Structural Vaccinology
- Nanoparticles
- GMMA
- RNA Vaccines
- Therapeutic mAbs

Per fare un vaccino:
- *Isolare il virus*
- *Crescerlo*
- *Inattivarlo*
- *iniettarlo*

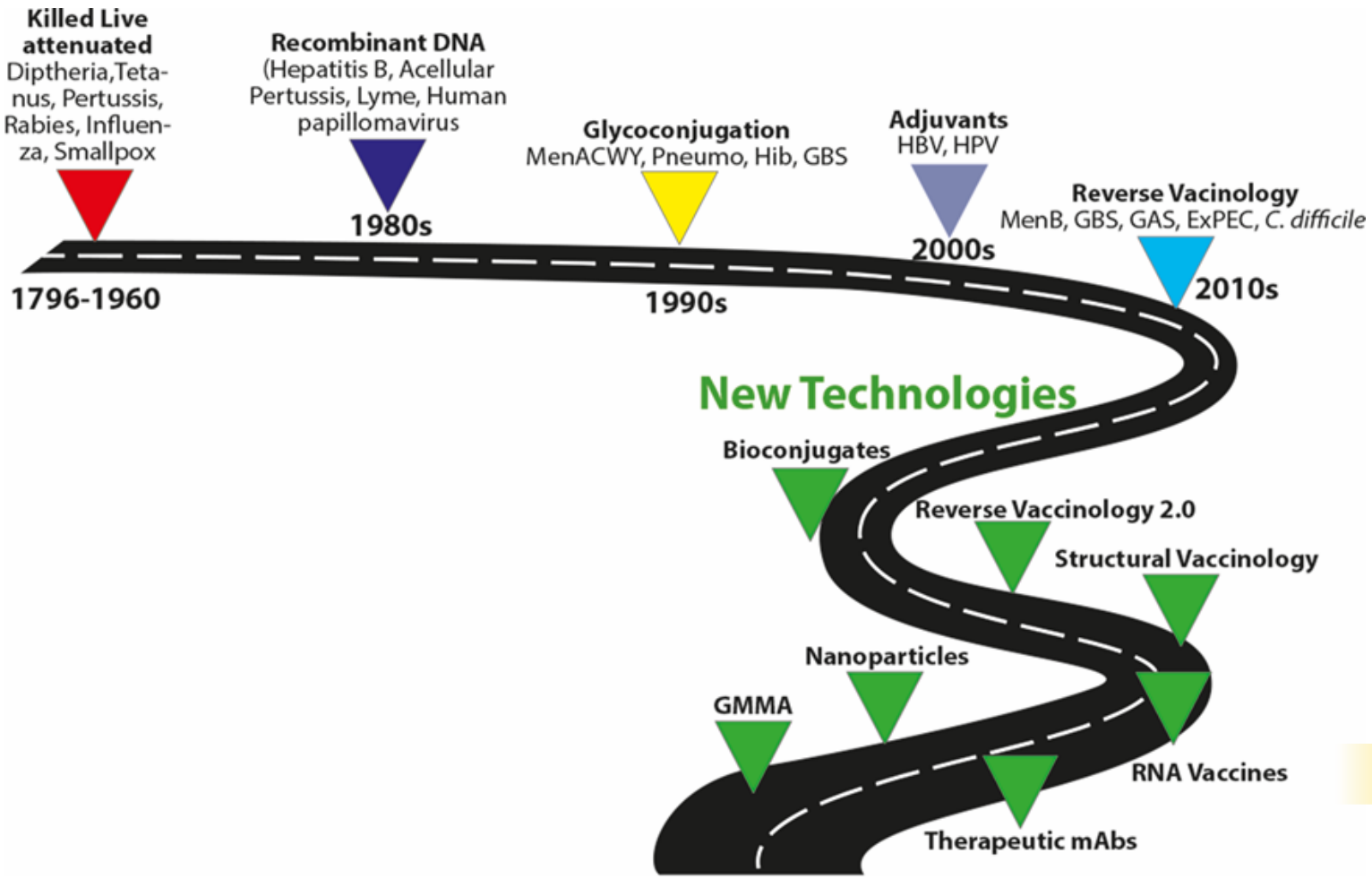


Source: Rosini R, Necchi S, Pizza M, Rappuoli R.. Frontiers in immunol 2020

Covid-19 vaccines
convergence of four modern technologies

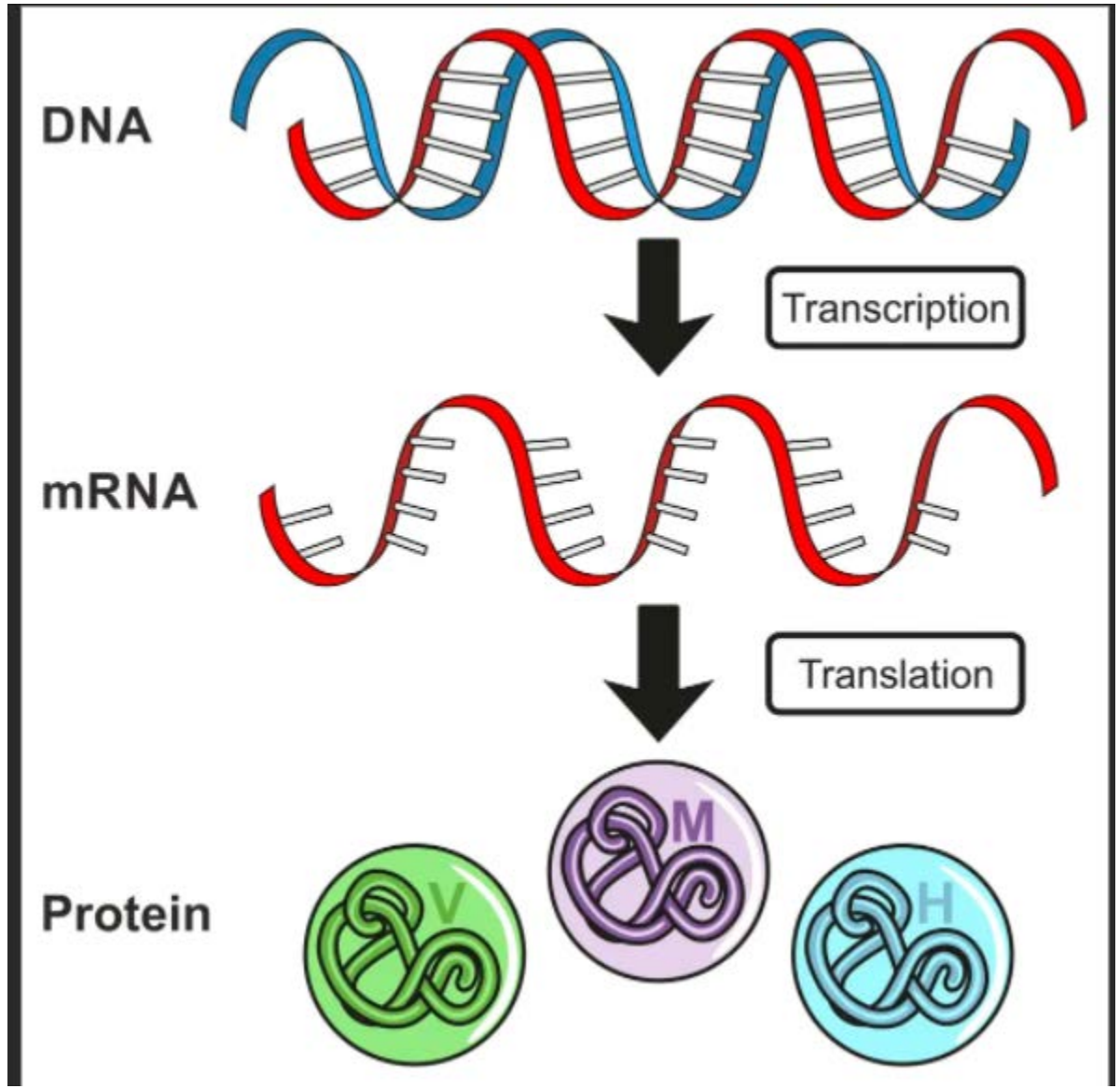


New technologies led to the development of new vaccines and will allow to conquer new diseases



RNA and viral vectors

- Source: Rosini R, Necchi S, Pizza M, Rappuoli R.. Frontiers in immunol 2020


DNA
Transcription
mRNA
Translation
Protein
V
M
H

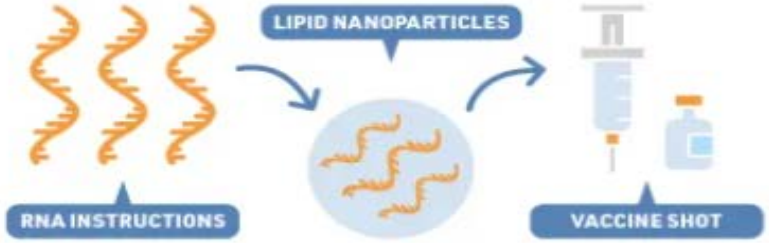
WHAT ARE RNA VACCINES?

SARS-CoV-2

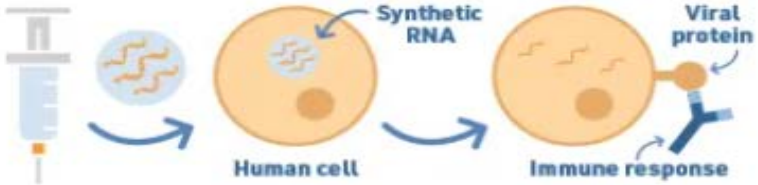
Viral RNA
The virus's genetic material. Contains instructions for making proteins.

Spike protein
Protein which helps the virus penetrate cells and initiates an infection.

The genetic code of the SARS-CoV-2 virus is made up of RNA. Scientists isolated the part of this genetic code that contains the instructions for making the virus's spike protein.



Synthetic RNA which codes for the virus spike protein is packed in lipid nanoparticles (very small fat droplets). This stops our bodies' enzymes breaking it down and helps our cells take it in.



Once the synthetic RNA is inside one of our cells, the cell follows the RNA instructions to produce the virus spike protein. Its production then triggers an immune response in our bodies.

RNA VACCINES: BENEFITS AND CHALLENGES

VACCINE PRODUCTION

RNA is easy to make in a lab, so RNA vaccines can be developed quicker than other vaccines.

SAFETY OF THE VACCINES

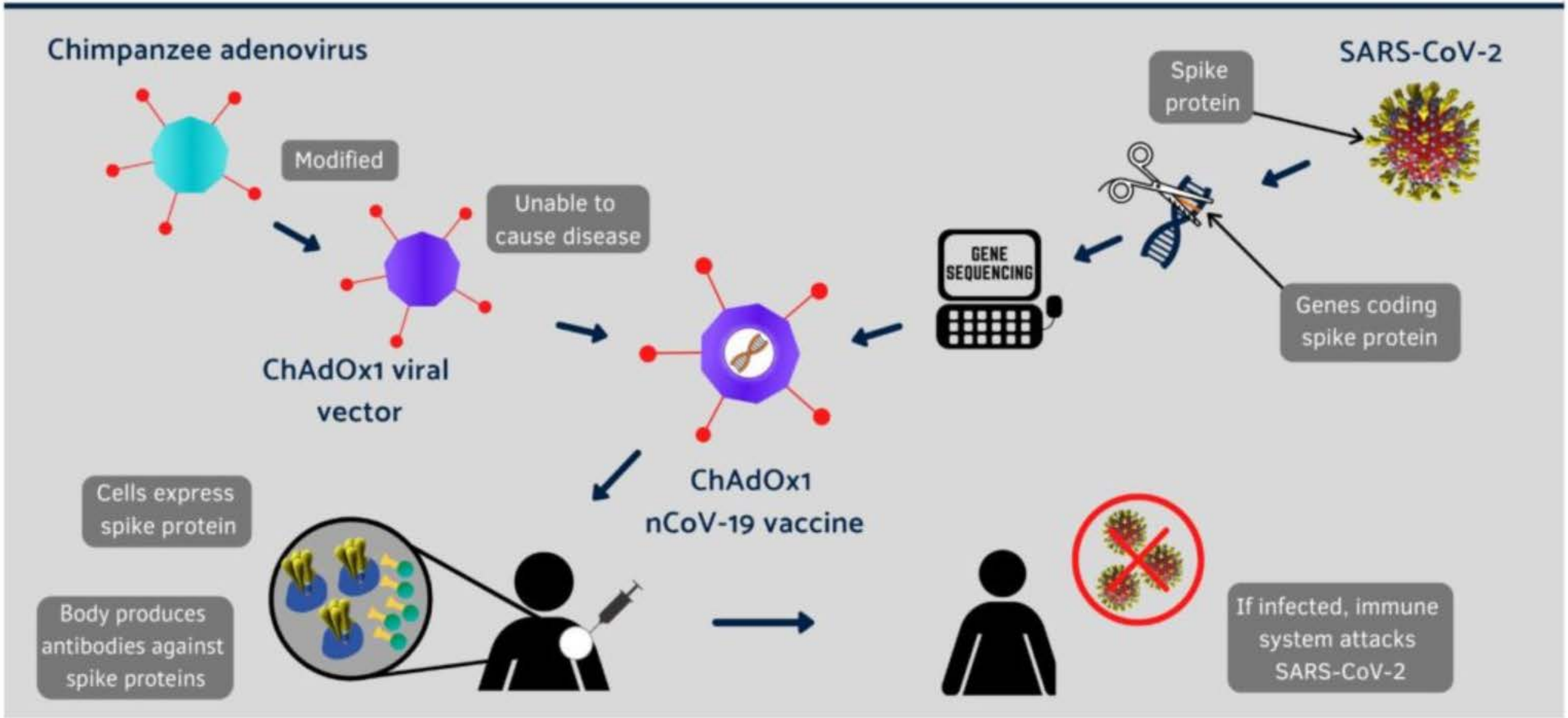
RNA can't cause infection and is broken down by normal processes in our cells. An RNA vaccine hasn't been licensed for use in humans before but they've been under development for several years for other viruses, including influenza, HIV, and Zika.

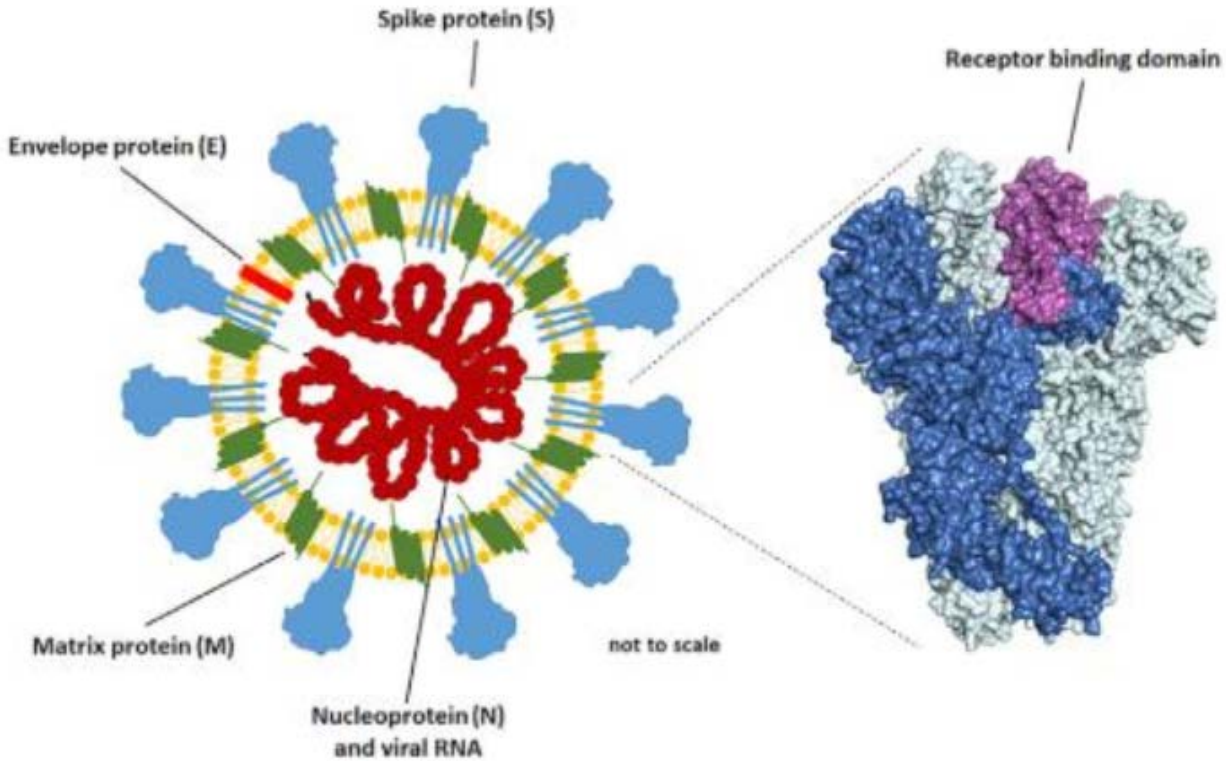
STORAGE AND TRANSPORT

Some RNA vaccines must be stored at low temperatures to remain stable, which makes storage and transport more challenging.

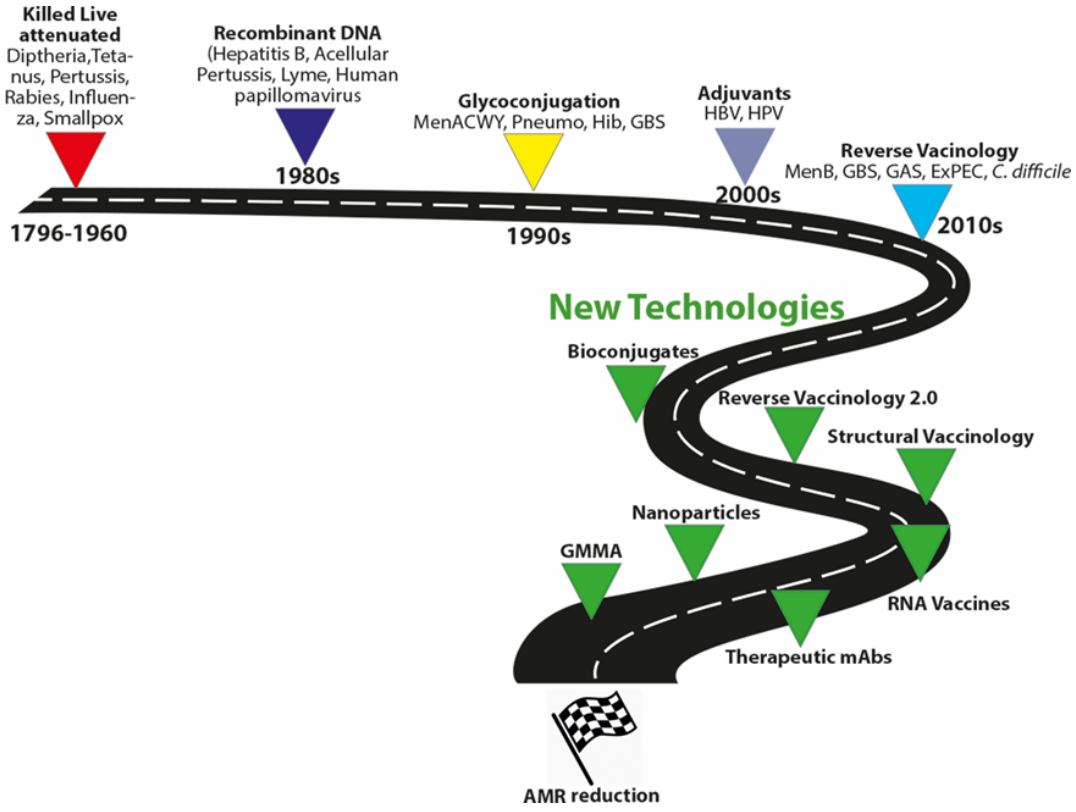
ROYAL SOCIETY OF CHEMISTRY

COVID-19 Oxford Vaccine Trial




Spike protein (S)
Receptor binding domain
Envelope protein (E)
Matrix protein (M)
not to scale
Nucleoprotein (N)
and viral RNA

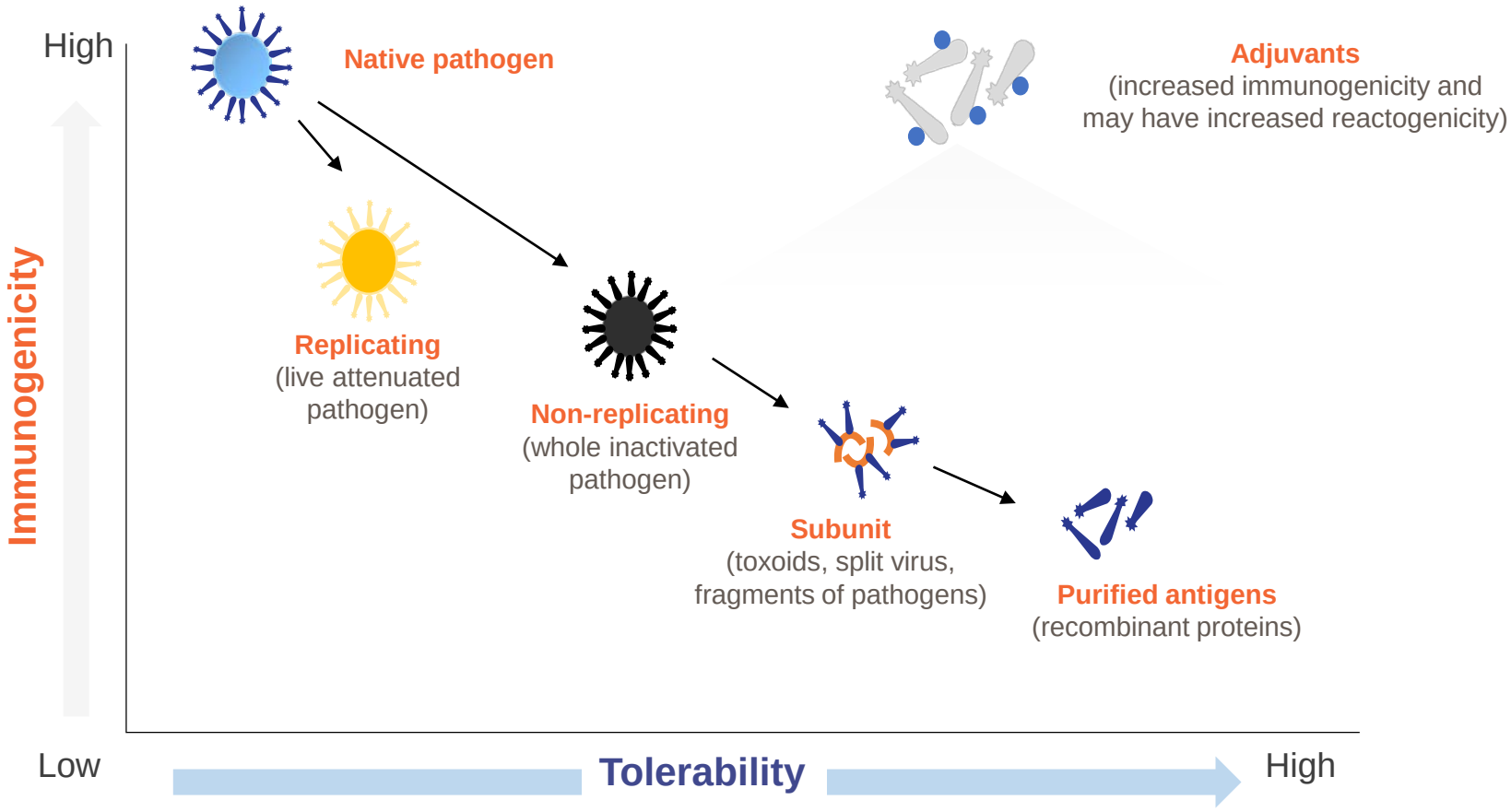
New technologies led to the development of new vaccines and will allow to conquer new diseases



Adjuvants

- Source: Rosini R, Necchi S, Pizza M, Rappuoli R.. Frontiers in immunol 2020

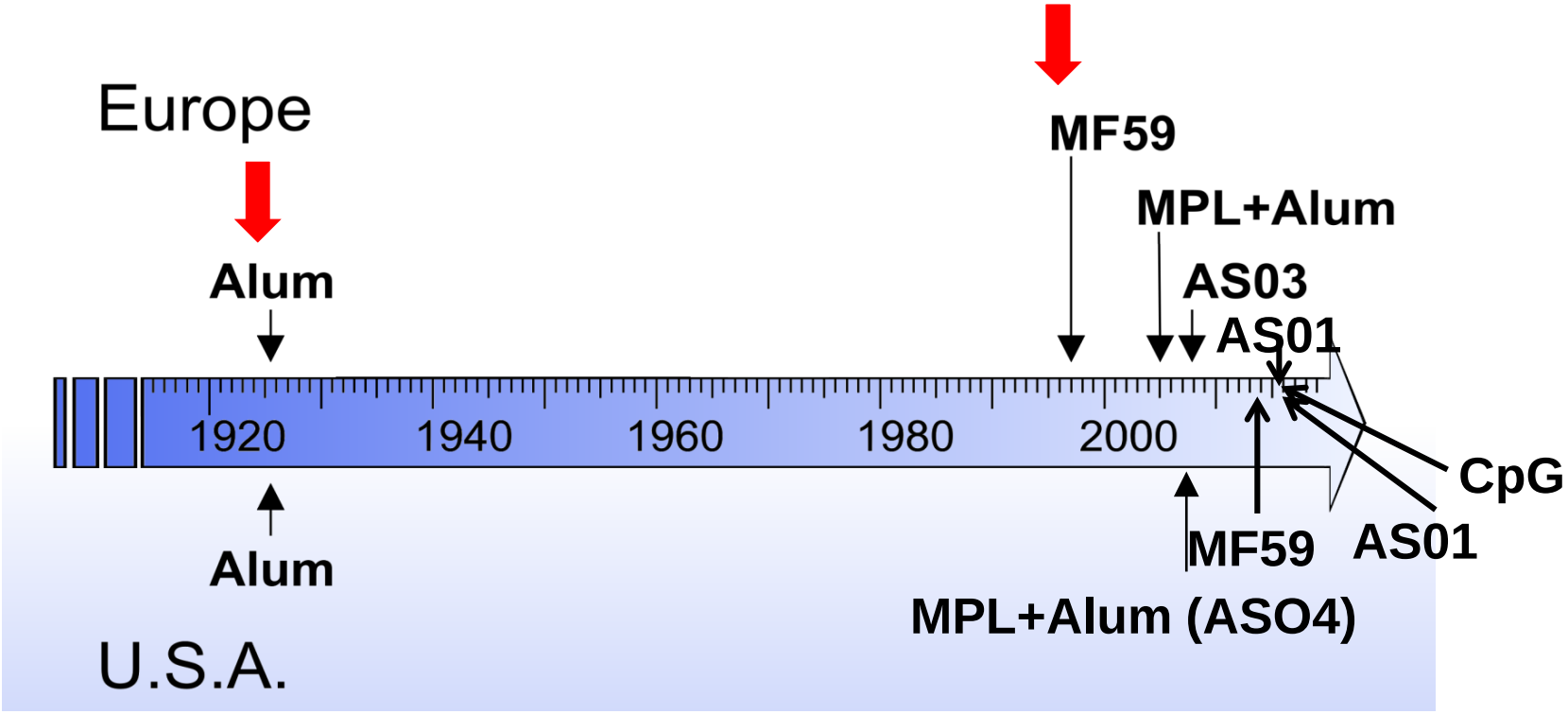
Why do we need adjuvant in some vaccines

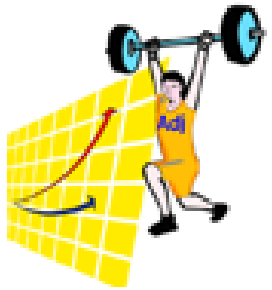


Illustrative figure based on Strugnell R *et al*. 2011; Garçon N *et al*. 2011

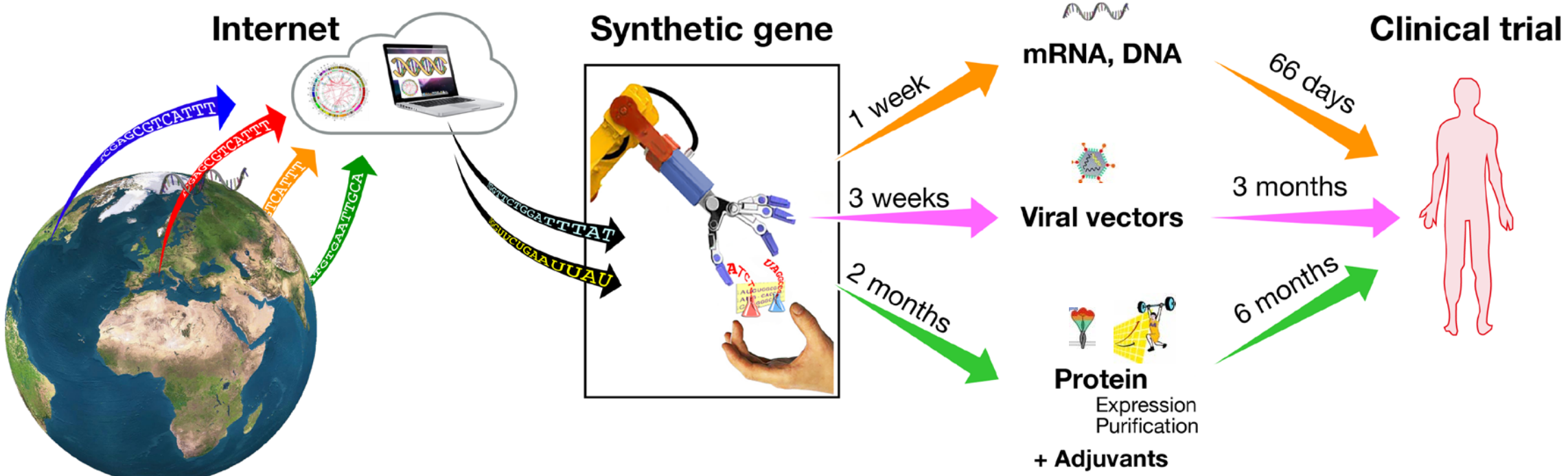
Strugnell R *et al. Perspect Vaccinol* 2011;1:61–88; Garçon N *et al. Perspect Vaccinol* 2011;1:89–113 (content on slide from pp. 61, 71, 72, 75, 76, 89, 111)

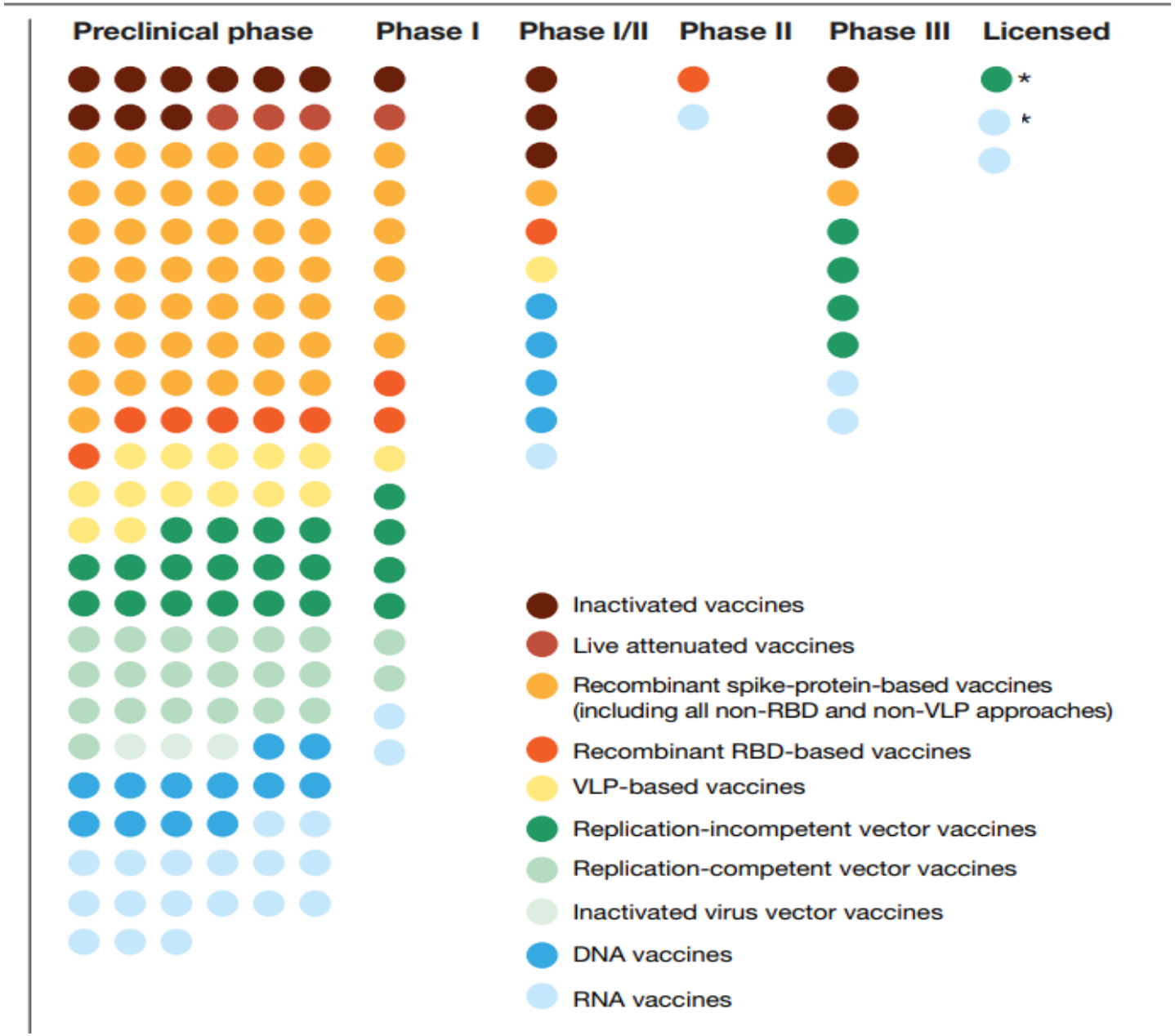
Adjuvants

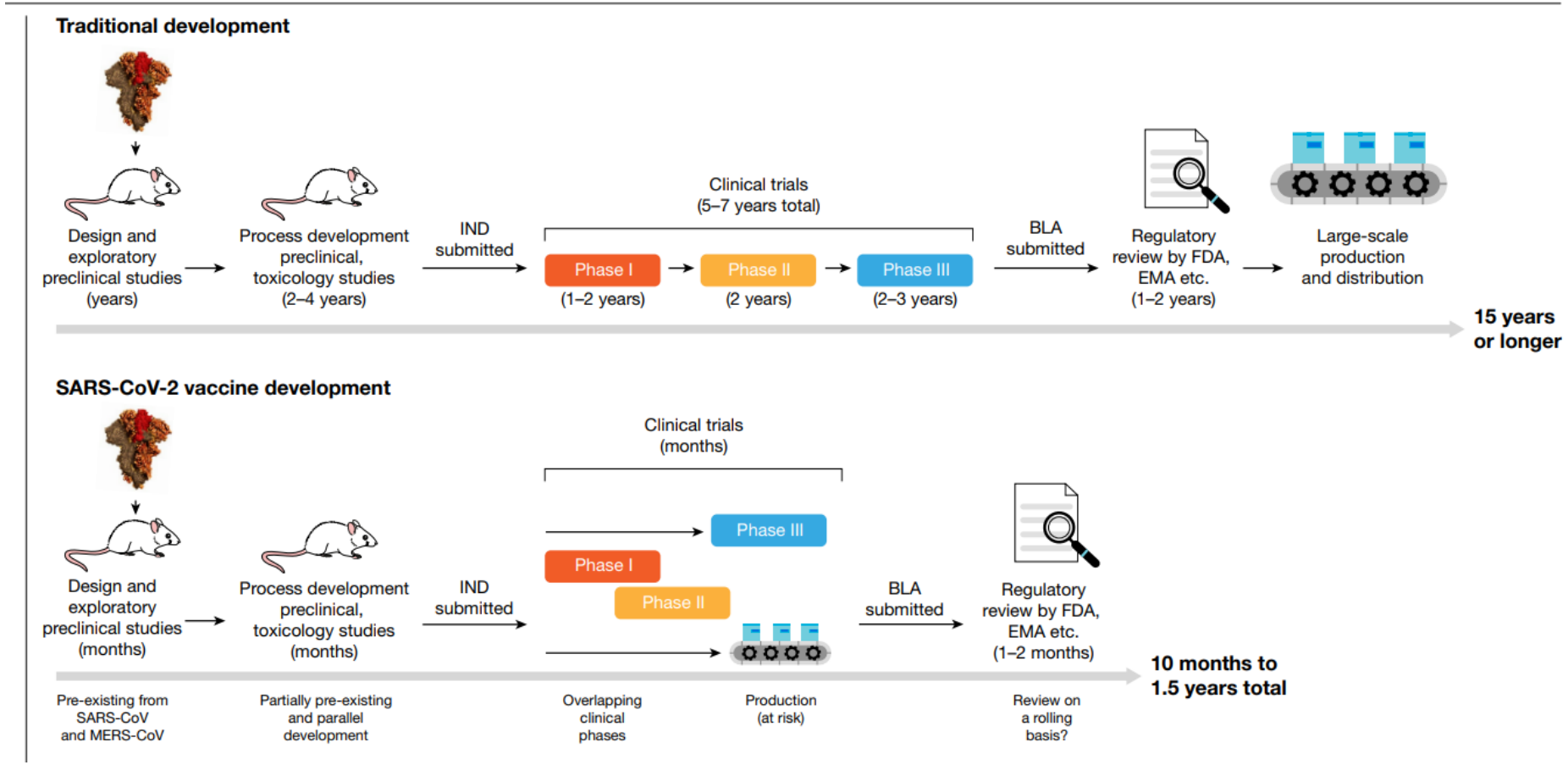

Europe
Alum
MF59
MPL+Alum
AS03
AS01
1920
1940
1960
1980
2000
CpG
Alum
MF59
AS01
MPL+Alum (ASO4)
U.S.A.



Three main vaccine types for Covid-19
more than 320 vaccines described




Preclinical phase
Phase I
Phase I/II
Phase II
Phase III
Licensed
*
*
Inactivated vaccines
Live attenuated vaccines
Recombinant spike-protein-based vaccines
(including all non-RBD and non-VLP approaches)
Recombinant RBD-based vaccines
VLP-based vaccines
Replication-incompetent vector vaccines
Replication-competent vector vaccines
Inactivated virus vector vaccines
DNA vaccines
RNA vaccines



Review

SARS-CoV-2 vaccines in development

https://doi.org/10.1038/s41586-020-2798-3
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Accepted: 17 September 2020
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Florian Krammer[1]✉

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in late 2019 in China and is the causative agent of the coronavirus disease 2019 (COVID-19) pandemic. To mitigate the effects of the virus on public health, the

- **Operation Warp Speed** (**OWS**) is a public–private partnership initiated by the U.S. government to facilitate and accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics.
- The program promotes mass production of multiple vaccines, and different types of vaccine technologies, based on preliminary evidence, allowing for faster distribution if clinical trials confirm one of the vaccines is safe and effective.
- Operation Warp Speed, initially funded with about $10 billion from the CARES Act (Coronavirus Aid, Relief, and Economic Security) passed by the United States Congress on March 27, is an interagency program that includes components of the Department of Health and Human Services, including the Centers for Disease Control and Prevention, Food and Drug Administration, the National Institutes of Health, and the Biomedical Advanced Research and Development Authority (BARDA); the Department of Defense; private firms; and other federal agencies, including the Department of Agriculture, the Department of Energy, and the Department of Veterans Affairs.
- Operation Warp Speed was formed to encourage private and public partnerships to enable faster approval and production of vaccines during the COVID-19 pandemic
- The name was inspired by terminology for faster-than-light travel used in the *Star Trek* fictional universe, evoking a sense of rapid progress. Operation Warp Speed uses BARDA as the financial interface between the U.S. federal government and the biomedical industry. The program was initially being funded with $10 billion with additional funds allocated through BARDA. Funding was increased to about $18 billion by October 2020.

Name	Technology	Amount	Date announced	Vaccine candidate	Notes
Johnson & Johnson (Janssen Pharmaceutical)[24][25][26]	Non-replicating viral vector	$1 billion	August 5, 2020	Ad26.COV2-S	This is in addition to $456 million the government awarded in March 2020.[27][28]
AstraZeneca–University of Oxford[29] and Vaccitech[30]	Modified chimpanzee adenovirus viral vector	$1.2 billion	May 21, 2020	AZD1222	
Moderna[22][23][30]	mRNA	$1.53 billion	August 11, 2020	mRNA-1273	The government had already given Moderna two grants of $483 million and $472 million.[31] The $1.53 announced on August 11 brings the total investment to $2.48 billion.
Novavax[32][33][34]	SARS-CoV-2 recombinant spike protein nanoparticle with adjuvant	$1.6 billion for advance commercial-scale manufacturing	July 7, 2020	NVX-CoV2373	Funding to demonstrate commercial-scale manufacturing; federal government will own the 100 million doses produced, but will be made available for clinical trials
Merck and IAVI[35][36]	Replicating viral vector Themis (measles) IAV(vesicular stomatitis)	$38 million	April 15, 2020	V590	V590 is Merck's collaboration with IAVI. Merck has another vaccine candidate, V591, which it acquired in May 2020 with Themis.
Sanofi and GlaxoSmithKline[37]	Protein (insect cell lines) with adjuvant	$2.1 billion	July 31, 2020	No name as of October 2020[38]	On December 11, 2020, the companies announced that they would delay the vaccine's release until late 2021 because it produced "insufficient immune response" in elderly people.[39]

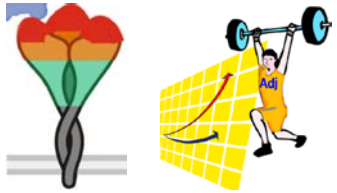
90
VACCINE CANDIDATES

243
TRIALS

12
APPROVED VACCINES

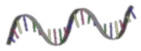
Three main vaccine types for Covid-19
Immunogenicity

Spike + adjuvant



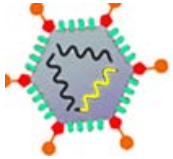
Novavax, Sanofi/GSK, Clover/GSK, Medicago/GSK

RNA

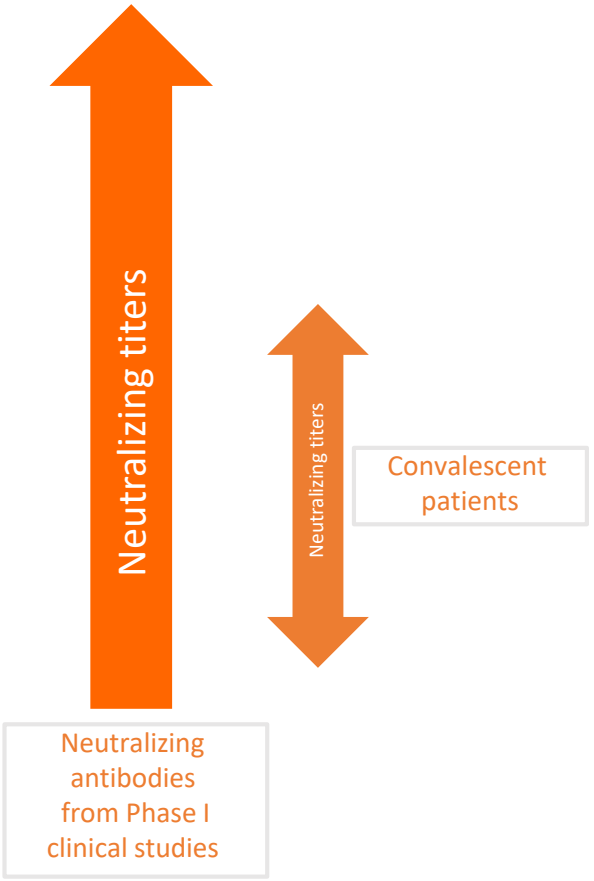


Moderna, BionTech/Pfizer, Curevac

Viral vectors



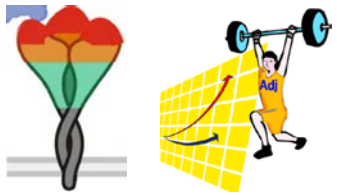
Oxford/Astra Zeneca, J&J, Reithera
Russian Vaccine, Chinese vaccines



Three main vaccine types for Covid-19
Immunogenicity

95% efficacy !!!
press release November 9th

Spike + adjuvant



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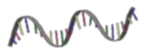
RNA



Moderna, BionTech/Pfizer, Curevac

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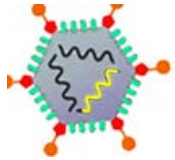
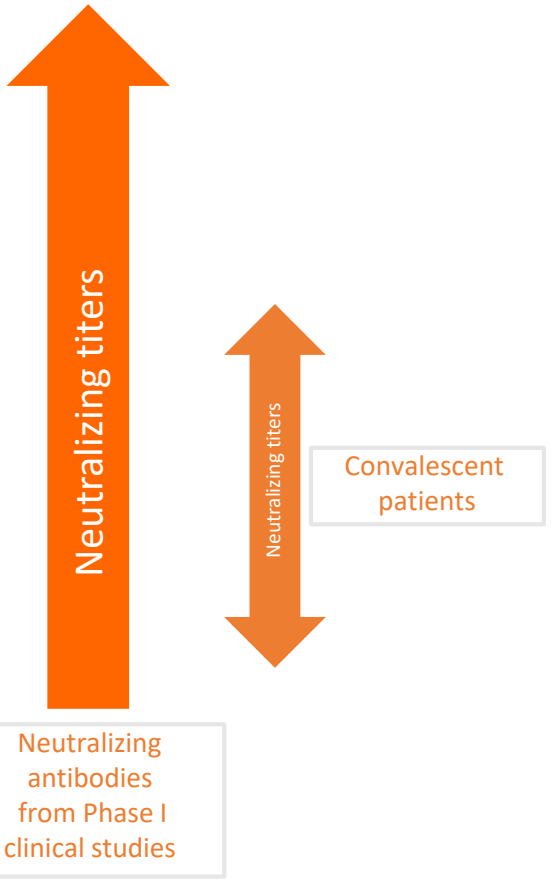


Oxford/Astra Zeneca, J&J, Reithera
Russian Vaccine, Chinese vaccines

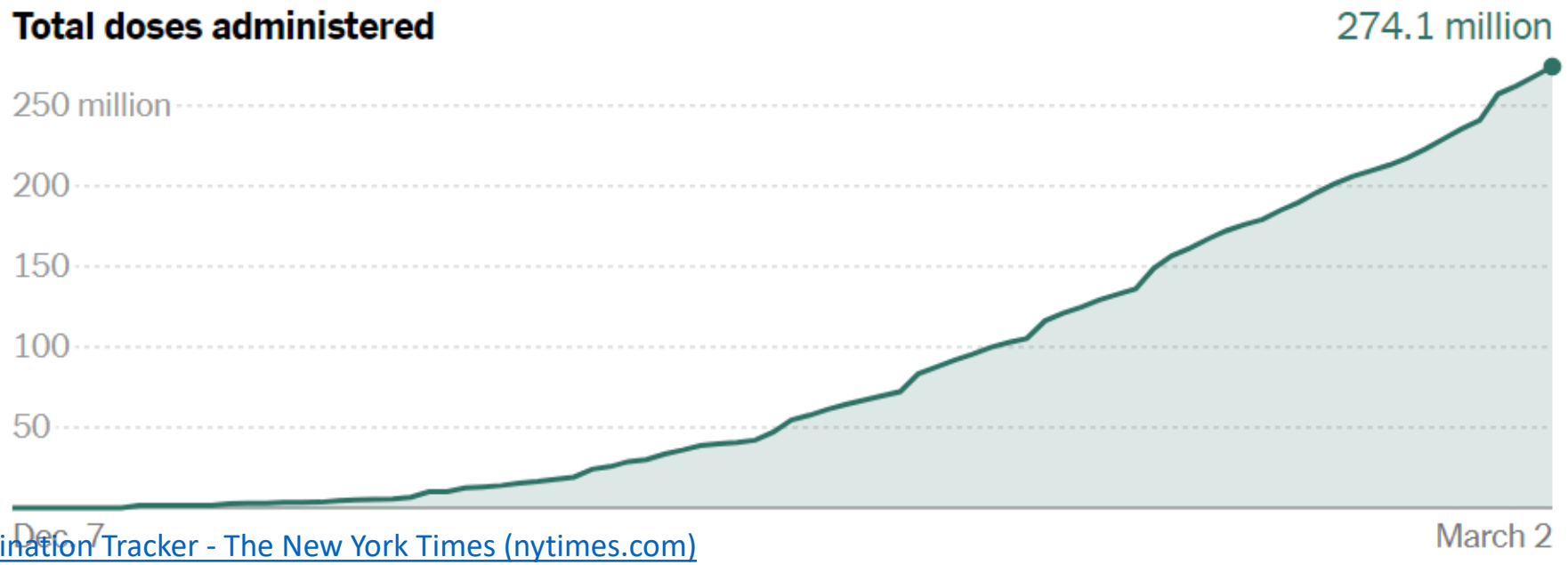
1 dose 62%
1 low + 1 High dose 90%



U.S.A. World Health

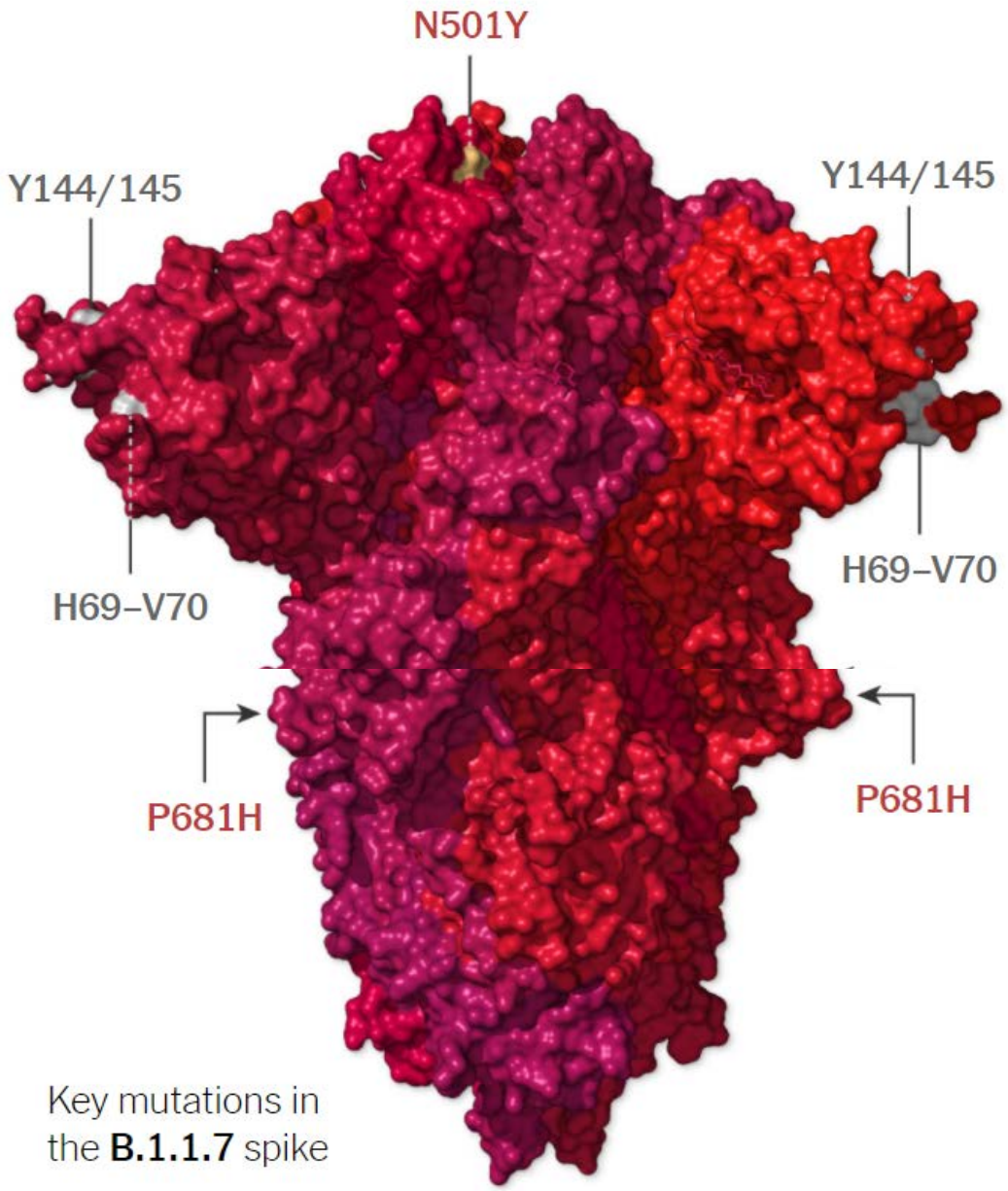
Tracking Coronavirus Vaccinations Around the World

By Josh Holder Updated March 4, 2021

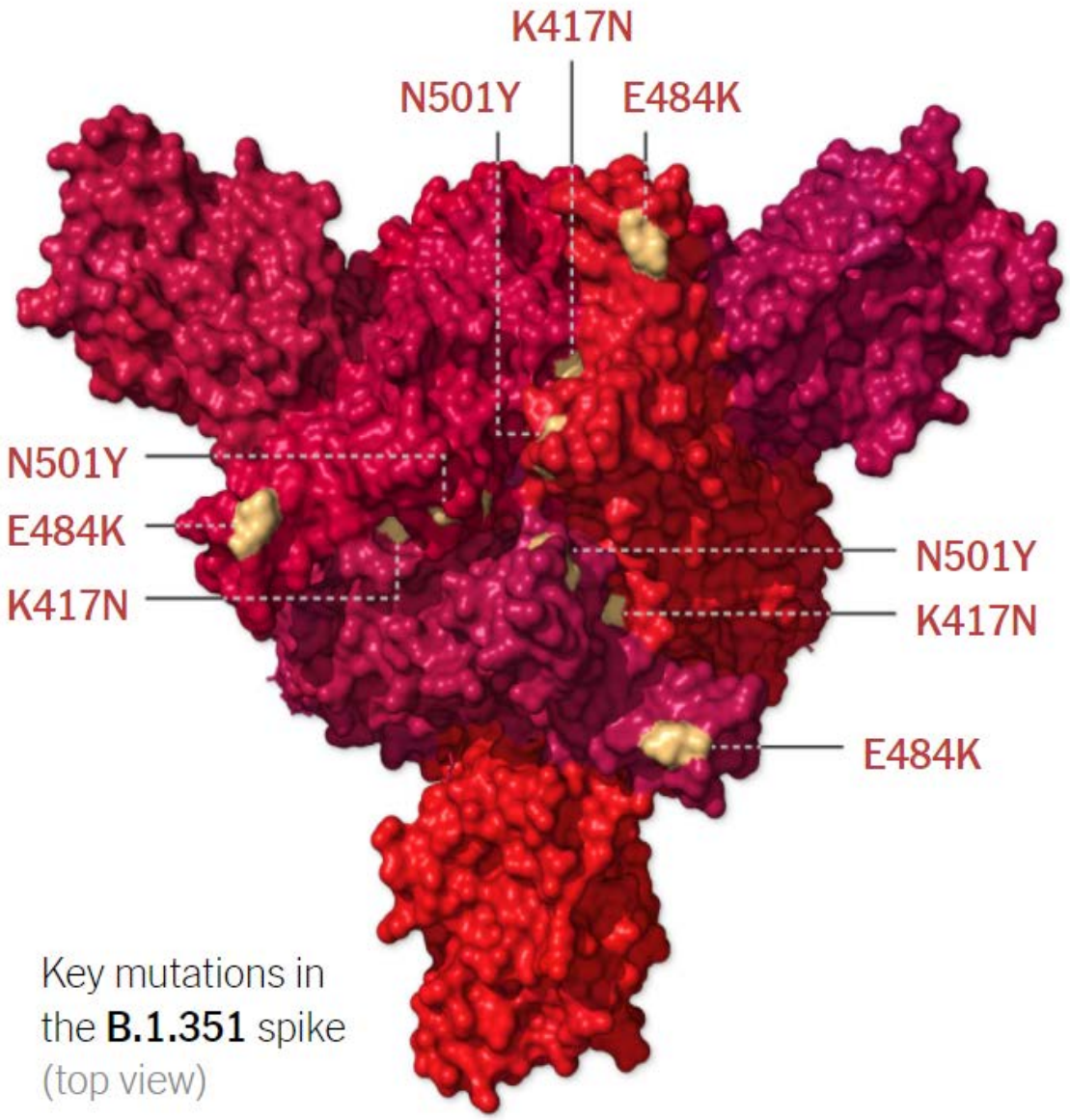


Covid World Vaccination Tracker - The New York Times (nytimes.com)

	Doses administered		Pct. of population	
	▼ Per 100 people	Total	Vaccinated	Fully vaccinated
World	**3.6**	274,186,339	–	–
Israel	95.0	8,436,312	54.7%	40.3%
Seychelles	82.8	80,131	57.8%	25.0%
U.A.E.	64.0	6,168,330	–	–
U.K.	32.5	21,599,027	31.1%	1.3%
Maldives	25.1	129,424	–	–
United States	24.3	80,540,474	15.9%	8.1%
Serbia	22.0	1,535,274	14.3%	7.7%
Chile	21.1	3,960,845	20.0%	1.1%
Bahrain	19.4	303,962	19.4%	–
Malta	17.4	84,129	11.2%	6.2%
Barbados	13.5	38,615	13.5%	–
Morocco	11.4	4,105,862	10.4%	1.0%
Italy	7.9	4,757,890	5.4%	2.5%
Belgium	7.4	845,113	4.6%	2.8%
France	7.2	4,839,444	4.7%	2.5%



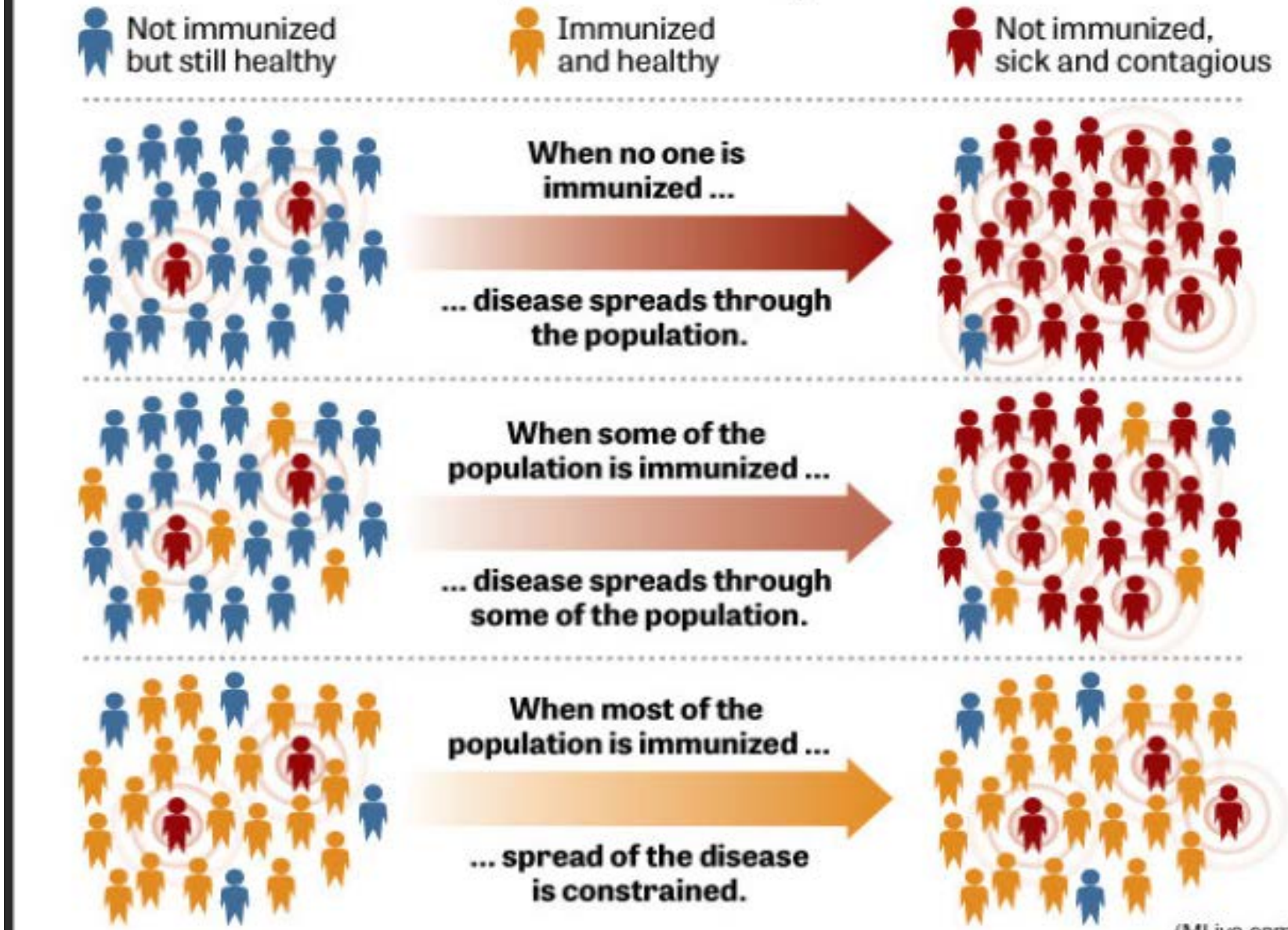
Key mutations in the **B.1.1.7** spike

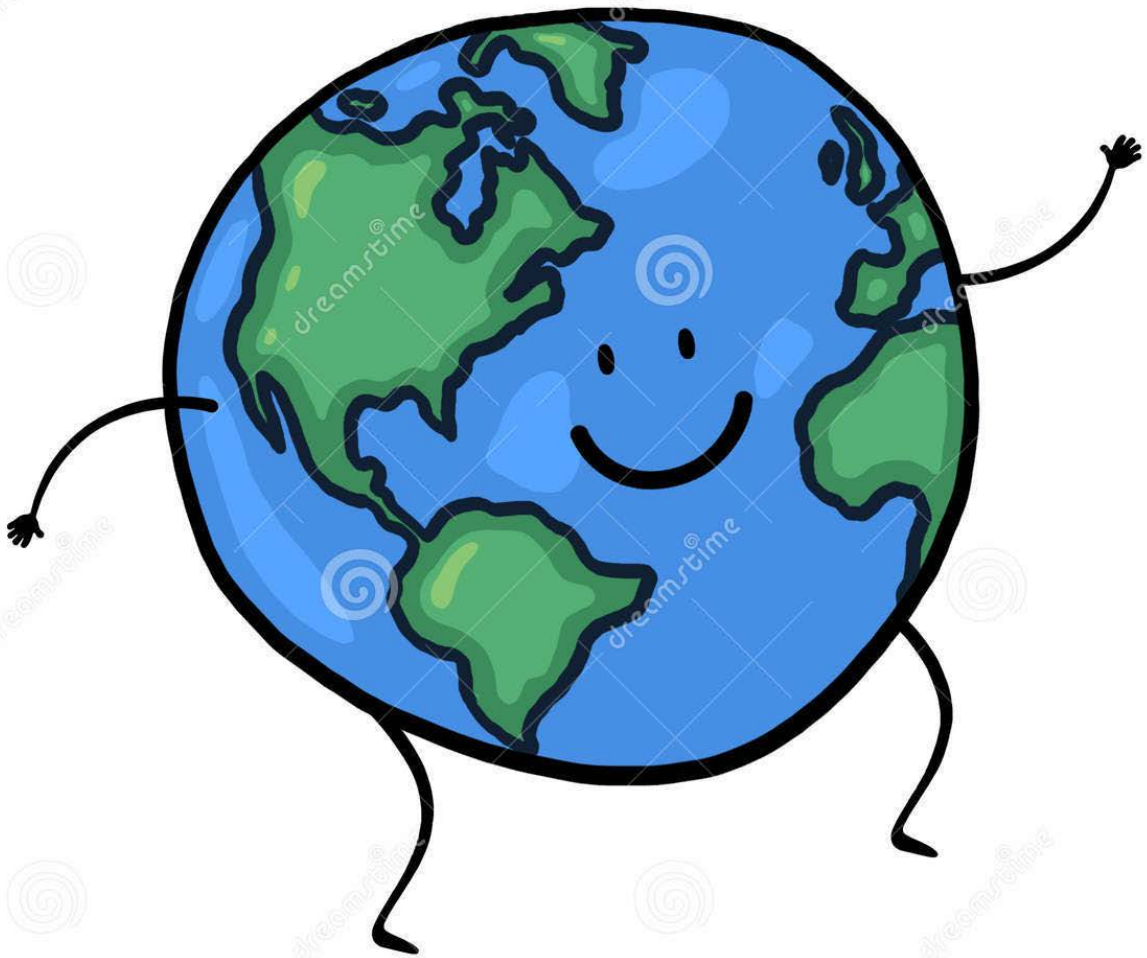


Key mutations in the **B.1.351** spike (top view)

WHY DOES MY CHOICE MATTER TO OTHERS?

It matters because of the concept of "herd immunity." Here's how it works:





Sperando di riconquistare presto la libertà.

Sperando in un mondo libero dalle malattie infettive

GRAZIE