GUPTA STRATEGISTS

Promise of vaccination:

is it the hoped for 'get out of COVID-jail card' ?

September 2021

Agenda

The development of COVID-19 vaccine is an inspiring story, however…

In practice the impact of the COVID-19 vaccine so far is equivocal

Promise of vaccination: what should we expect in the long term?

COVID-19 vaccine is an inspiring story, 30% of the global population being vaccinated in less than 2 years since the virus emerged

Phases of vaccine development

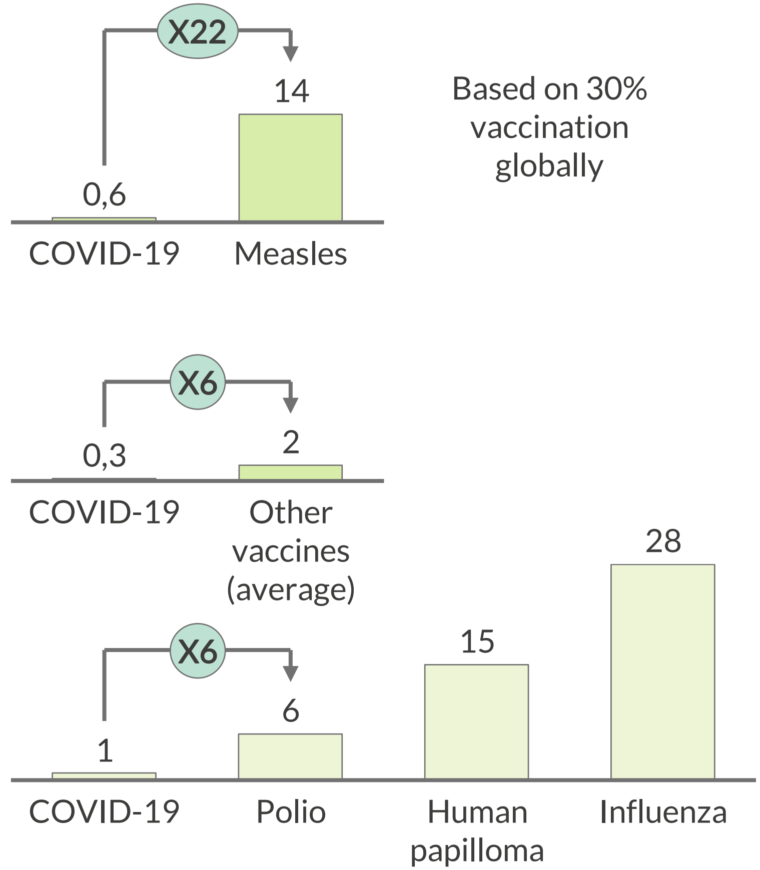
Operate: The vaccine is distributed and given to inhabitants across the globe

Manufacture: Vaccine is produced in large commercial quantities, with extensive quality tests

Design Phase I,II,III: Vaccine is developed and tested, first on animals, and subsequently on humans (in three phases with expanding groups sizes, and focus shifting from lab safety to field efficacy)

COVID-19 vaccines: design, manufacture and operate

[years[1]]



1) Colarossi (2020) How long it took to develop 12 other vaccines in history
2) Petri (2021) COVID-19 vaccines were developed in record time – but are these game-changers safe?
3) Smith et al (20212) Vaccine production, distribution, access and uptake
Source: Our world in data, Worldbank, Analysis Gupta Strategists

Within months of discovering the virus the first candidate vaccines had been produced in lab, thanks to decades of fundamental research

Novel 2019 coronavirus genome

edward_holmes
Jan '20
10th January 2020
…The sequence has also been deposited on GenBank (accession MN908947 30.6k) and will be released as soon as possible.
Update: This genome is now available on GenBank and an updated version has been posted 30.6k.

Disclaimer:
Please feel free to download, share, use, and analyze this data. We ask that you communicate with us if you wish to publish results that use these data in a journal. If you have any other questions – then please also contact us directly.
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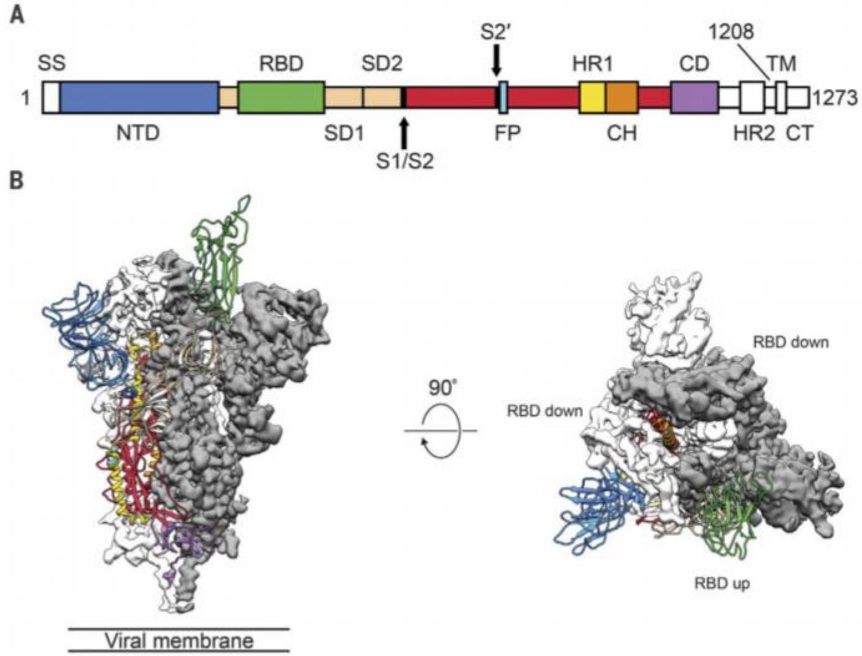
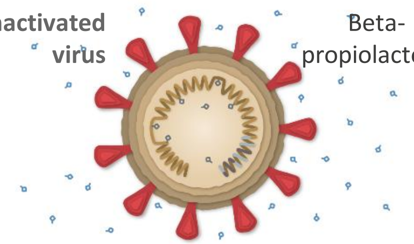


Fig. 1. Structure of 2019-nCoV S in the prefusion conformation. (**A**) Schematic of 2019-nCoV S primary structure colored by domain. Domains that were excluded from the ectodomain expression construct or could not be visualized in the final map are colored white. SS, signal sequence; S2', S2' protease cleavage site; FP, fusion peptide; HR1, heptad repeat 1; CH, central helix; CD, connector domain; HR2, heptad repeat 2; TM, transmembrane domain; CT, cytoplasmic tail. Arrows denote protease cleavage sites. (**B**) Side and top views of the prefusion structure of the 2019-nCoV S protein with a single RBD in the up conformation. The two RBD down protomers are shown as cryo-EM density in either white or gray and the RBD up protomer is shown in ribbons colored corresponding to the schematic in (A).

10 Jan was genome sequence published in open source and 13 March Cyro-EM (3,5 A resolution) images revealed the binding mechanism

Using different technology platforms different countries around the world have been equally successful in rapid development of vaccines

Inactivated Corona Virus
Sinovac, Sinopharm, Covaxin



- Extract virus from humans
- Grow it is large numbers(e.g. monkey kidney)
- Deactivate the virus (leave protein intact)
- Mix with adjuvant

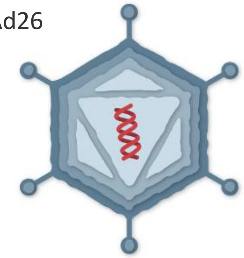
- One of the oldest technologies (Salk polio vaccine)

- Phase III in Brazil, Turkey, Indonesia, Chile and India (25k+27k)).

- Double dose, easy storage

- Probably highest global market share ~40-60% = 1 billion doses
- China, India, Brazil….

Viral Vector - Adenovirus
Sputnik V, AstraZeneca, Serum, Janssen



- Gene for coronavirus spike protein created
- Add the gene to an Adenovirus (Simian)
- Engineered vectors that can invade cells but not replicate

- First approved for use Johnson vaccine for Ebola (2020)

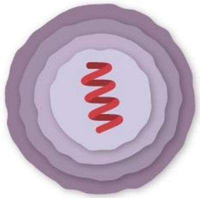
- Phase III in UK, Brazil, India (24k+21k)

- Single, Double dose, easy storage

- Global market share 15-25%

- India, UK, Russia,

mRNA
Pfizer BioNTech, Moderna



- Nucleoside –modified RNA for coding spike protein (prefusion state locked thru 2 proline mutations)
- Trap fragile RNA in lipid nanoparticles

- First application ever

- Phase III in US, Brazil, S. Africa (44k+30k)

- Double dose, cold storage

- Global market share ~ 20-30%

- USA, EU

Testing of the candidate COVID-19 vaccine took less than a year

Design of COVID-19 vaccine: Example mRNA vaccines, other candidate vaccines had nearly similar timelines

Genetic structure of virus published
11 January

Binding mechanism of spike protein published
13 March

Phase I: 2 months

Start phase I/II trial of Moderna
15 March

Results Phase I/II trial of Moderna
14 July

Phase II: 4 months

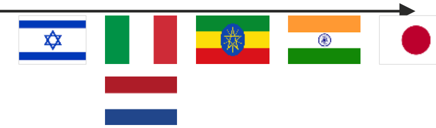
Start phase III trial of Moderna
27 July

Results Phase III trial of Moderna
30 Dec

Phase III: 5 months

Approval of vaccine: Israel was first to approve
19 Dec
14 Feb

< 1 year approval



Source: analysis Gupta Strategists

To ensure speed, manufacturing and supply chain readiness was done in parallel with trials, resulting in availability even before approvals

Supply Chain of US manufacturing of Pfizer/BioNTech mRNA COVID-19 vaccine

Grow DNA and testing	Transport to a different plant	Transcribe and purifying of mRNA	Transport to a different plant	Encapsulate and testing	Global Shipping

Grow DNA and testing

- Cloning DNA in batches/vats from E.Coli resulting in trillions of DNA plasmids
- Filtration of plasmids
- Linearization (enzymes cutting circles)
- Bagging
- Testing (no extraneous material)
- Extraction

Transcribe and purifying of mRNA

- 40l vessels (enzymes and chemicals) to build mRNA strands from DNA plasmids
- 10 million vaccine doses per batch
- 4 batches a week
- Filtration
- Storage in frozen bags (10 m doses)

Encapsulate and testing

- Lipid nanoparticles made in high-speed mixers with an ethanol and lipid mixture
- This had been the major bottleneck in the initial scale-up
- Packing in 6 dose vials
- 1-3 million doses per batch
- 40 quality-control measures

110 days (1-3 million doses per batch)

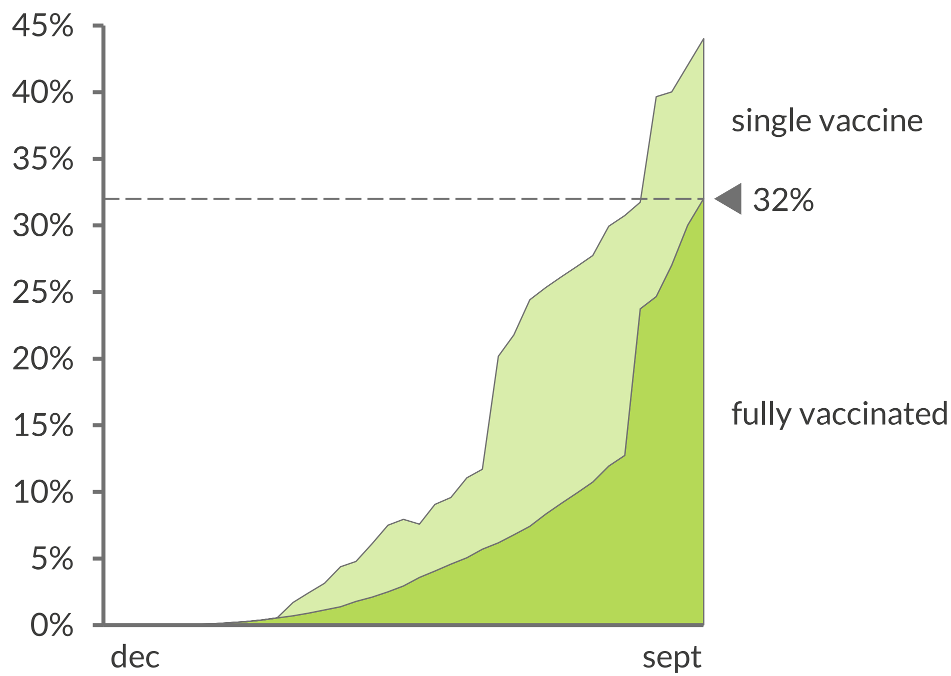
60 days (production goal)

Production time Influenza vaccine 540 days

1) Vaccineseurope.eu
Source: Analysis Gupta Strategists

1/3rd of the global population has been vaccinated in less a year which is order of magnitudes faster than any vaccination ever

Vaccination coverage of COVID



Vaccination coverage compared to other programs

- It took 14 years to reach measles vaccination coverage globally what has been achieved for COVID-19 vaccination in 9 months (30% coverage)
- The speed of COVID-19 vaccination roll-out remains order of magnitude faster than any vaccination programs ever: one month (Aug-Sept) uptake for COVID was comparable to what took years to achieve for measles worldwide

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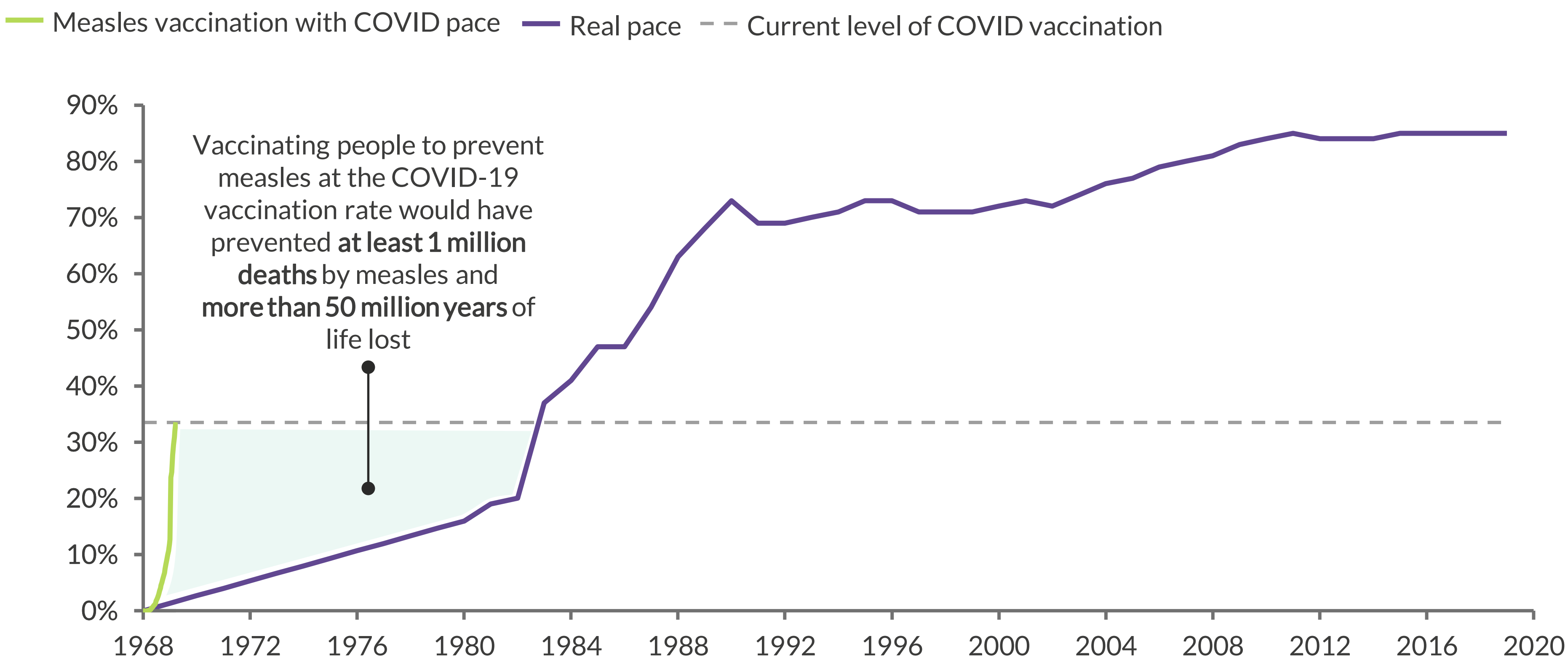
1) Total number of people who received all doses prescribed by the vaccination protocol (Our world in data) divided by the world population (Worldbank)

Source: Our world in data, Worldbank, analyses Gupta Strategists

A COVID paced vaccination improves outcomes drastically

Vaccination coverage of COVID in comparison to measles
[x-axis: time (Dec '20 – Oct '21 for COVID, 1968-2020 for measles), y-axis: vaccination coverage]



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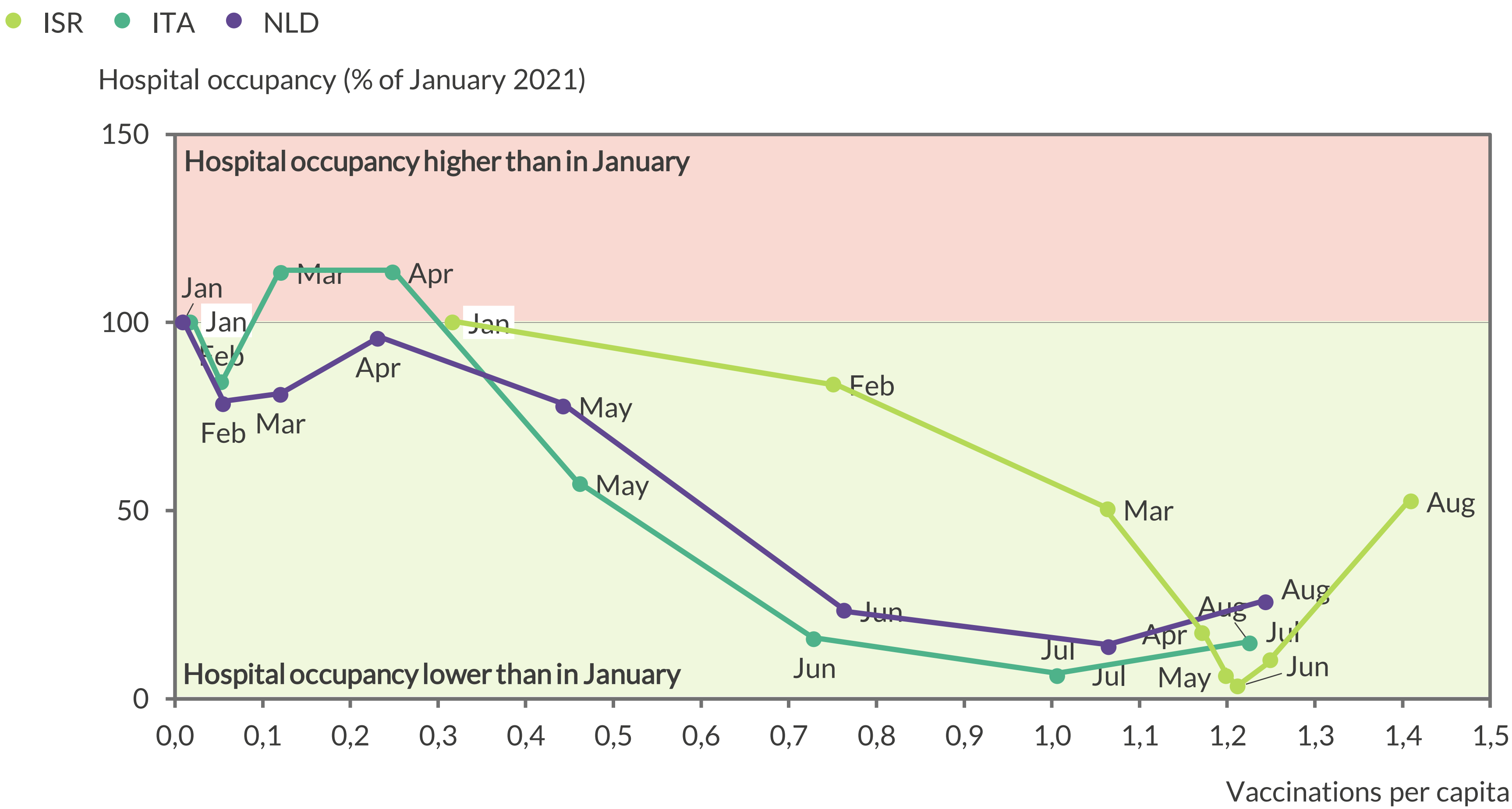
In practice the impact of the COVID-19 vaccine so far is equivocal

Promise of vaccination: what should we expect in the long term?

After an initial decline, there is a concerning rise in COVID-19 hospitalization despite high vaccination rates

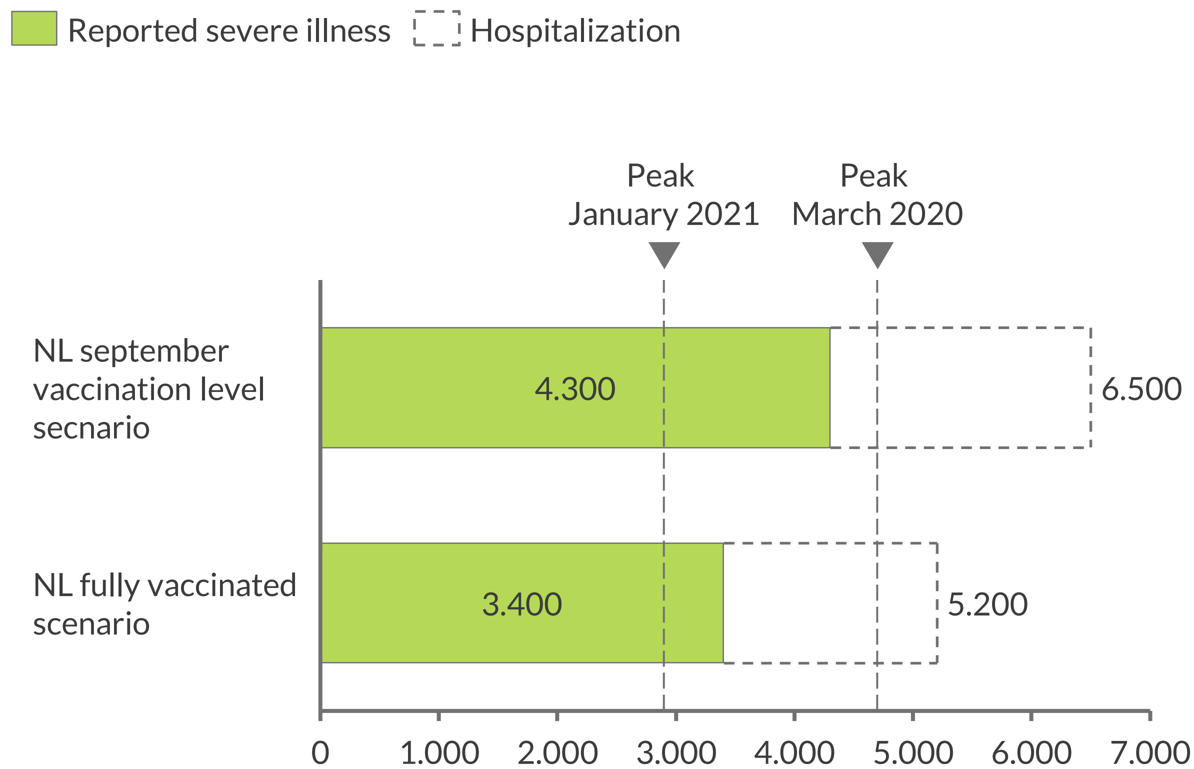
Change in hospital admissions and vaccination rate
[January 2021 – July 2021, per country, normalized to 100 at start date in Jan]



Source: Our World In Data, analysis Gupta Strategists

How successful is vaccination in preventing hospitalization? Israel experience projected to NL situation provides a sobering picture

Projected hospital occupancy (incl. ICU) for two scenarios in the Netherlands based on Israel data
[Total hospital occupancy, # patients]



Israel situation projected on NL[1,2,3]
[hospital occupancy in two scenarios]

- If we project the September 2021 situation in Israel (outbreak with all measures considered) on the Netherlands, the projected hospital occupancy could become twice as high as in January 2021.
- If we look at the hypothetical situation in which the total Dutch population is vaccinated two times, the projected hospital occupancy could still become 1,5 times as high as in January 2021

1) Both scenarios are projections of the Israelian situation corrected for population size, age and vaccination rate.
2) Bandwidth is the difference between number of patients classified by Israel as 'severely ill' and number extrapolated to 'in hospital' where 'severely ill' is the lower and 'in hospital' is the upper bandwidth.
3) Both scenarios are based on the current situation in Israel, all measures (including mild lockdown) considered. We did not take the possible intensification of measures into account.
Source: : UN Population Prospects 2019, Our World In Data, Israelian COVID dashboard, RIVM, data from 08-09-2021, analysis Gupta Strategists

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Promise of vaccination: what should we expect in the long term?

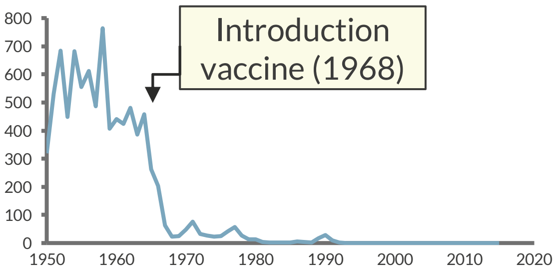
Based on comparison of COVID-19 disease characteristics to other diseases and vaccinations suggests a limited impact scenario as likely

Eradicated

Several vaccinations have been highly successful. Vaccines have (nearly) eradicated child diseases like measles and pox.

COVID-19 has limited similarity to these diseases, which have[1] :
- low mutation rate
- imitable immune response

Diseases eradicated
[Measles cases US, x1000, 1950-2015]

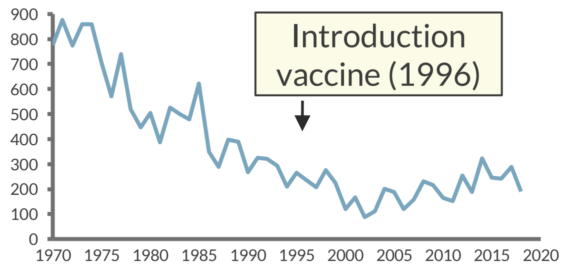


Limited

Some vaccines have shown to decrease the disease burden, yet not enough to erase the disease. An example is the influenza vaccine.

COVID-19 **has many shared characteristics with influenza[2,4]:**
- high mutation rate
- hard to imitate immune response

Diminishing diseases
[Influenza incidence NL, 1970-2020]

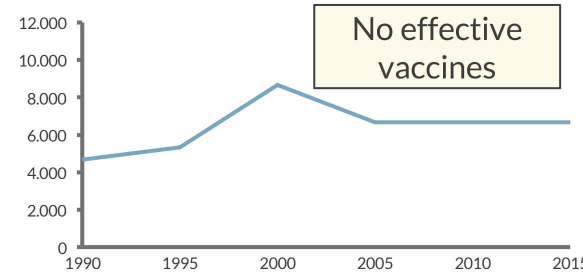


None

A well-known example of the lack of effective vaccines, despite decades of research, is the battle against the HIV virus.

COVID-19 **differs largely** from HIV, which has[3]:
- extremely high mutation rate
- lack of natural immune system response

No impact on diseases
[HIV cases UK, x1000,1990-2015]



1) Woudenberg et al. 2017. Large measles epidemic in the Netherlands, May 2013 to March 2014: changing epidemiology
2) CDC, 2021.
3) Gupta et al. 2020. Evidence for HIV-1 cure after CCR5Δ32/Δ32 allogeneic haemopoietic stem-cell transplantation 30 months post analytical treatment interruption: a case report, *Lancet*

Source: Nature, ourworldindata.org, analysis Gupta Strategists

Footnotes

1)Fulton et al. 2015. Mutational analysis of measles virus suggests constraints on antigenic variation of the glycoproteins. *Cell Reports*,
2)Sanjuan, R. , Nebot, R., Chirico, N, Mansky, L, Belshaw, R., Viral Mutation Rates, *journal of virology*, 2020
3)Levy et al. 2020. Optimal priming of poxvirus vector (NYVAC)-based HIV vaccine regimens for T cell responses requires three DNA injections. Results of the randomized multicentre EV03/ANRS VAC20 Phase I/II Trial, *PLoS Pathog*
4)A J McMichael, A.J., Rowland-Jones, S.L. 2001. Cellular immune responses to HIV, *Nature*
5)Gazit et al. 2021. Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections
6)Gupta et al. 2020. Evidence for HIV-1 cure after CCR5Δ32/Δ32 allogeneic haemopoietic stem-cell transplantation 30 months post analytical treatment interruption: a case report, *Lancet*
7)WHO. 2008, WHO Immunological Basis for Immunization Series
8)Krammer, F. 2019. The human antibody response to influenza A virus infection and vaccination. *Nat Rev Immunol* 19, 383–397